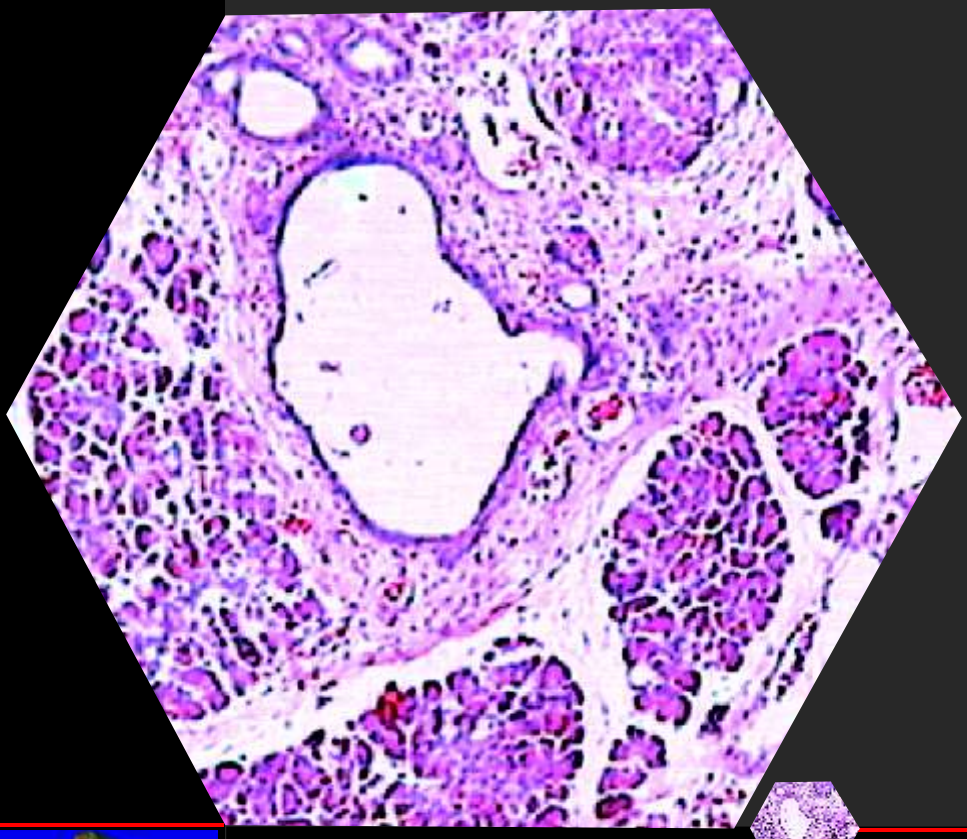

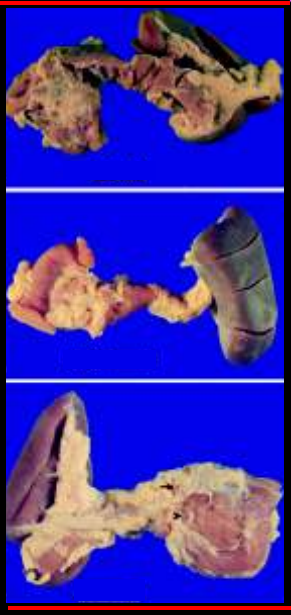

Chronic pancreatitis and pancreatic diabetes in India

Balakrishnan, Harish Kumar,
Sudhindran, Unnikrishnan

Chronic Pancreatitis and Pancreatic Diabetes in India

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Preface

Chronic pancreatitis is a worldwide disease and one of its major complications is diabetes mellitus. In the western world the commonest cause of this disease is alcohol abuse. We also know that a frequent cause of recurrent acute pancreatitis is gall stone disease. The Marseille, Cambridge and Atlanta symposia have all tried to define and classify pancreatitis. From the earlier view evolved at the Marseille symposium that acute and chronic pancreatitis are different diseases, we have come a long way and now most workers tend to agree that acute pancreatitis could progress to chronic pancreatitis. In fact, it is still a matter of some debate whether the first lesion in alcoholic pancreatitis is an acute or a chronic one. The discovery of the genetic mutations in hereditary pancreatitis by Whitcomb and colleagues has given a new dimension to these debates. The several reports of genetic mutations associated with alcoholic pancreatitis and idiopathic pancreatitis from the West have created a lot of excitement among workers in this field.

Fifty years ago Zuidema described a group of young malnourished diabetics from Indonesia who also had pancreatic fibrosis and calcification. Subsequent reports of this disease from different parts of Asia and Africa among the malnourished youth of poor tropical countries earned this condition recognition as a separate disease entity and the sobriquet of " tropical pancreatitis". Because of the peculiar characteristics of this disease and its differences from alcoholic pancreatitis, this entity attracted worldwide attention. The largest number of patients of tropical pancreatitis has been described from the small south-west state of Kerala in India. Originally thought to be restricted to the south of India, there are now reports of tropical pancreatitis from many other regions of India (even outside the strict definition of " tropics"). The etiology of this disease remains an enigma till today. In 1985, the World Health Organization brought out a Technical Report on Diabetes Mellitus in which they described the entity of malnutrition related diabetes with its subgroups of fibrocalculous pancreatic diabetes (FCPD) and protein deficient pancreatic diabetes (PDPD). FCPD reflected the diabetologist's view of tropical pancreatitis.

In 1987 a National Workshop on Chronic Pancreatitis in India was organised by Balakrishnan at Trivandrum under the auspices of the Indian Society of Pancreatology, bringing together workers from all over India, to share their experience on chronic pancreatitis in different parts of the country. The proceedings of this workshop, edited by Balakrishnan, were published as a monograph, "Chronic Pancreatitis in India", by the Indian Society of Pancreatology. This book brought out, for the first time, a comprehensive review of the disease in India, and was acclaimed globally by the fraternity of workers in the field of pancreas.

Much has happened in the area of pancreatitis research after this publication. Newer definitions, classifications, tools for investigations, animal models, insight into the molecular mechanisms of the initiation of the earliest pancreatic injury, the role of cytokines and the work on genetic mutations in pancreatitis (PRSS1, SPINK1 and CFTR) have all taken the frontiers of pancreatic research to hitherto unknown territories. In the light of all these developments, we thought it is time to take a fresh look at pancreatitis in India and see what has ensued during the past several years, and particularly, what has happened as far as epidemiology and etiology of chronic pancreatitis is concerned. A National Workshop on Tropical Pancreatitis / Fibrocalculous Pancreatic Diabetes in India was conducted at the Amrita Institute of Medical Sciences and Research Center, Cochin from 17 to 19 December, 2004. All the participants were requested to contribute chapters detailing their experience and views on chronic pancreatitis, to a book, which was subsequently going to be published. The result is this book. We offered the authors a certain degree of liberty with their articles in size, format, presentation and opinion. This book is a true reflection of the divergent observations of different workers, their controversial views and hypotheses. We deliberately wanted to present controversies, to make this a starting point in our further search for the truth. Is the 'tropical pancreatitis' some of the workers describe really tropical pancreatitis, or simply idiopathic pancreatitis? How do you define tropical pancreatitis? Does the old definition still hold good? Are there fundamental differences between alcoholic pancreatitis and tropical pancreatitis? Does cassava have any role in the etiology? Why

is the natural history of tropical pancreatitis changing? Are tropical pancreatitis and fibrocalculous pancreatic diabetes the same disease or different diseases? Is it a pancreatitis or a pancreatopathy? What is the role of genetic mutations? In trying to answer questions, this book raises fresh question after question. It reflects the conflicting views and observations of workers in this large subcontinent on a baffling clinical problem.

There is a stimulating article by Whitcomb on the possible interactions between different "domains" of toxins, genes and altered immunity in the causation of recurrent acute pancreatitis and the role of recurrent acute pancreatitis in the progression to chronic pancreatitis. Balaraman Nair propounds his hypothesis that it is an atrophy of the pancreas with little inflammation, in tropical pancreatitis. Sandhyamani, with her feeding experiments in monkeys, shows that it is the imbalance between proteins and carbohydrates in the diet that leads to pancreatic injury.

Azad Khan shares with us his experience in FCPD in Bangladesh and examines its relationship with tropical calcific pancreatitis. Mohan and Eesh Bhatia describe the endocrine changes in tropical pancreatitis/FCPD. They advance their arguments about whether tropical pancreatitis and fibrocalculous pancreatic diabetes are the same disease or are different diseases. Balakrishnan examines the changes that have occurred, over the years, in the clinical picture and behaviour in tropical pancreatitis and suggests that it is, perhaps, time to redefine tropical pancreatitis.

Chandak presents the largest series of genetic mutations in pancreatitis reported from the subcontinent. Tripathy describes his vast experience with malnutrition related/modulated diabetes mellitus. An array of eminent pancreatic surgeons such as Sikora, Wig, Sudhindran, Ramesh and Mohapatra share their experiences, preferences and results of surgery.

There are many other chapters, by Choudhuri, Garg, Roop Rai, S.P. Singh, Unnikrishnan, Ganesh Pai, Varghese Thomas and Nagalotimath, describing the varied spectrum of the disease, all illuminating and interesting, as you read on.

Despite all these uncertainties, we have gathered a huge amount of data on the occurrence of tropical pancreatitis in India. We have clear descriptions about its pathology. The work of Sandhyamani has opened a new area for further research. There are preliminary data coming in from different parts of the country on genetic mutations in the disease. We are able to care for our pancreatic diabetics much better now than before and they live longer. We are trying out newer endoscopic modes of therapy. Over the years, our surgeons have accumulated a vast store of experience in optimizing surgery in chronic pancreatitis and developing standardized surgical procedures. These are all areas in which progress has been made. We would like to work and arrive at the etiology/etiological factors of this disease and device early preventive measures, if feasible.

Many have helped us in bringing out this book. This is a publication of the Indian Pancreatitis Study Group. We wish to specially thank **Biocon Limited** who readily agreed to sponsor this book and the Printers, **L.G. Creations, Bangalore,** for the excellent job they have done. Mr. N. Sudhakaran, Secretary, Institute of Digestive Diseases, Amrita Institute of Medical Sciences, Cochin deserves our special thanks for the commendable secretarial assistance rendered. This book, we are afraid, may be having a few technical flaws, for which we would appeal to the readers to bear with us.

Cochin,
India,
2006

V. Balakrishnan
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Chapter 1

The changing paradigm of chronic pancreatitis

David C Whitcomb

Summary

Identification of mutations that lead to pancreatitis and its complications has revolutionized our understanding of pancreatic diseases. Integrating the pathologic effect of a gene mutation on the function of key proteins, and understanding the role of these proteins from a systems biology approach will lead to changes in every aspect of medical care. With few exceptions, all forms of pancreatitis are traced back to disregulation of trypsin. Trypsin controls trypsin, and calcium flips the switches between trypsin mediated activation and inactivation. Mutations in the calcium regulatory domains of trypsinogen (PRSSI) lead to calcium-independent facilitation of activation or prevention of inactivation. Mutations in the SPINK1 gene lower the threshold for unregulated trypsin activation of itself and other zymogens.

Mutations in CFTR, the molecule that regulates pancreatic duct secretion, diminish the ability to flush activated trypsin into the intestine, especially in the presence of distal duct resistance. Mutated PRSS1, SPINK1 and CFTR genes are susceptibility factors for recurrent acute pancreatitis (RAP), and only a subset of these subjects go on to chronic pancreatitis, which should be defined as a complication of RAP. Chronic pancreatitis requires alterations in three domains of risk: Environmental - metabolic stressors, diminished protection from trypsin activation and injury, and an altered immune response resulting in a strong anti-inflammatory response to injury with dominant fibrosis. We propose that patients with genetic susceptibility to recurrent acute pancreatitis be recognized as having RAP with interepisode resolution, or modified RAP with one or more altered or sustained responses to injury including: (A) anti-inflammatory predominant response with accelerated fibrosis, (B) B-type persistent pain, (C) calcific pancreas, and/or (D) diabetes.

Whether this paradigm applies to tropical pancreatitis remains to be determined. However, one possibility is that variations in idiopathic and tropical pancreatitis could be viewed through a new paradigm where tropical calcific pancreatitis (TCP) represents RAP with modifier domains A+B+C whereas fibrocalculous pancreatic diabetes (FCPD) represents RAP with modifier domains A+C+D. Future efforts are being directed toward early molecular diagnostics and developing strategies for intervention and prevention.

Introduction

Our knowledge of human pancreatic diseases arose from comparing clinical symptoms with pathologic abnormalities found at autopsy and abdominal x-ray. Classic studies of Chiari [1], Comfort [2], Zuidema [3] and others led to our first level of understanding, which was expanded, integrated and codified through consensus conferences in Marseille [4-6], Cambridge [7,8], and Atlanta [9] which defined and classified acute and chronic pancreatitis based on detailed clinical observations and review of human pathology [10]. The major clinical advances in understanding pancreatic diseases followed the breakthroughs in abdominal imaging with CT scans and ERCPs in the 1980's and MRCP and EUS in the 1990s which provided outstanding images of the pancreas, but did not provide insight into the etiology of the pancreatic diseases, nor long-term prognosis.

Many approaches have been used to determine the etiology of the pancreatic diseases, and each has strengths and limitations. Histology remains the gold standard for defining pathology, but this approach is limited by the danger of pancreatic biopsy [10]. Furthermore, anatomical pathology and histology only provide information about the location and nature of the pathological process (including stage and grade), but this reflects the down-stream results of the cause, (often at the end-stage of the process), and does not provide insight into the etiology unless a foreign body or infectious agent is identified. Imaging studies are surrogates for anatomical pathology. Epidemiology studies have likewise failed to identify all but mild or very weak risk factors, usually reflection of risk with odds ratios (OR) of 3 to 3. For example, alcohol consumption and tobacco smoking are clearly associated with chronic pancreatitis, but the probability of an average person developing chronic pancreatitis after exposure to either factor is very low[10]. These limitations have been recognized, and new approaches are needed.

Genetics may help provide *some* answers. Indeed, it has already provided break-through insights into the mechanisms of some forms of recurrent acute and chronic pancreatitis – in some populations - under some conditions. However, these insights have not yet been translated into effective interventions or preventative strategies for individual patients

– and especially those with "tropical pancreatitis". Progress has been made in understanding "idiopathic" chronic pancreatitis in the United States, and many of the new ideas and perspectives that the data has forced on the author will be presented.

The National Workshop on Tropical Pancreatitis (December 18-19, 2004 Kochi, India) was organized because (a) there is a major national problem with pancreatic diseases (b) there are many interested parties that share a vision of solving this specific problems and (c) new opportunities may be available to determine the scope and mechanism of this medical enigma. This chapter will focus on the challenges of prospectively addressing complex medical problems that have a genetic component, and discuss issues associated with performing studies in complex trait diseases.

Part 1 – The changing paradigm of idiopathic chronic pancreatitis in North America and India

What is chronic pancreatitis?

Chronic pancreatitis is a term that reflects the end-stage pathology of inflammation-associated diseases. Chronic pancreatitis should be distinguished form acinar cell hypofunction from Shwachman-Diamond Syndrome [11,12], pancreatic atrophy or loss of the pancreatic gland from surgery or other processes. Although end-stage chronic pancreatitis results in pancreatic exocrine insufficiency, all exocrine insufficiency is not caused by chronic pancreatitis. Unfortunately, the term chronic pancreatitis is used clinically to describe a wide variety of disorders with a few similar features of inflammation, destruction and fibrosis, and therefore can lead to confusion when clinical features of totally different diseases that are generally classified as "chronic pancreatitis" are lumped and compared. Our thinking has been further biased by the definitions of the Marseille meetings [4-6] which made a distinction between acute pancreatitis and chronic pancreatitis, implying that they are totally different disorders, and that when they are seen together, the acute pancreatitis is a consequence of chronic pancreatitis. This must be rejected. Instead, we should view acute pancreatitis as an *event*, and chronic pancreatitis as an inflammatory cell mediated destructive *process* that is dominated by fibrosis [13,14].

What do we actually know about the origin of chronic pancreatitis? First, we know that something happens within a person that causes a normal pancreas to progressively deteriorate into an end-stage, sclerotic pancreatic remnant over some period of time (Figure 1). Historically, this progression has been documented through autopsy studies and surgical biopsies leading to definitions of chronic pancreatitis based on histology [4,10]. Therefore, our clinical efforts reflect this historical perspective and are directed at *predicting histology* in living subjects using CT, ERCP, MRCP or pancreatic function test.

Our research group is also concerned that investigative studies comparing tissue from normal pancreas with tissue from subjects with chronic pancreatitis using arrays, proteomics or other techniques will never lead to an understanding of etiology, mechanism of progression or substantially improve prognosis (Figure 1) [13]. Comparative molecular and gene expression studies on pancreatic tissue will define histology, not etiology.

Human genetic studies revolutionized our understanding of the etiology and prognosis of chronic pancreatitis. The initial breakthrough came in 1996 with the genetic linkage studies in hereditary pancreatitis kindreds [15,16] and the molecular identification of mutations in the cationic trypsinogen gene (*PRSS1*) of these families [17]. Two additional genetic variations also are strong susceptibility factors for chronic pancreatitis – the serine protease inhibitor, Kazal type 1 gene (*SPINK1*) [18,19] and the cystic fibrosis transmembrane conductance regulator gene (*CFTR*). [20,21] However, as we focus on the physiology of these genes and the impact of the common mutations on protein function, we recognize that they are genes that *regulate trypsin activity* during synthesis, storage, secretion or transport out of the pancreatic duct. Trypsin is the key enzyme that regulates the activity of all of the other pancreatic zymogens, and if trypsinogen is activated inside the pancreas, it will lead to pancreatic injury through autodigestion. Theoretically, this should lead to *acute pancreatitis*, not chronic pancreatitis. Indeed, on reexamination, the known risk factors for chronic pancreatitis are also risk factors for recurrent acute pancreatitis. This leads us to advance the following hypothesis: chronic pancreatitis is a complication of recurrent acute pancreatitis (RAP) defined by extensive post-injury fibrosis. The process

of initiating the fibrosis process (SAPE hypothesis model) and the organization of risk factors (TIGAR-O) are presented elsewhere .[10, 14, 22]

Combining our knowledge of pancreatic physiology and mechanisms controlling intrapancreatic trypsin activity have provided the clues to understand chronic pancreatitis as a complex disease .[13] The new insights into the molecular mechanisms of acute and chronic pancreatitis have forced us to rethink the organization of information and development of new models for testing new hypotheses.

Taken together, the best model of chronic pancreatitis appears to reflect the convergence of three domains of risk (Figure 2) as a complex disorder . [13,14] In the first domain are the metabolic and environmental factors that increase the risk of trypsinogen activation. This is based on the recognition that patients with *PRSS1*, *SPINK1* or *CFTR* mutations do not have ongoing pancreatic injury, but rather metabolic- or environmental-factor stimulated attacks. The second domain includes genes that are mutated or other factors that limit the capacity of the pancreas to respond to injury. *Thus, the activation force is defined by domain one and the threshold for triggering an attack of acute pancreatitis is defined by domain two*. The frequency of insults that overcome the protective mechanisms therefore equals the frequency of recurrent acute pancreatitis. However, a *different* set of environmental and genetic factors controls fibrosis. This is an immune system-mediated process involving the macrophages, stellate cells, cytokines and related factors. Genetic and environmental factors that influence the immune response fall into domain 3. Thus, the factors that promote fibrosis or retard reabsorption of the matrix proteins determines the rate and severity of fibrosis in patients with recurrent acute pancreatitis.

What is tropical pancreatitis?

Tropical pancreatitis has been defined as a form of "idiopathic chronic pancreatitis", with unique epidemiological and clinical features. In the most simple terms tropical pancreatitis was described by Geevarghese as a disease with "pain in childhood, diabetes in puberty and death at the prime of life". A recent text book describes tropical pancreatitis as a form of chronic pancreatitis characterized by *recurrent abdominal pain*,

pancreatic *calculi*, and *diabetes mellitus*, occurring mostly among poor children and young adults of many developing nations.[23]

The initial abdominal pain is reminiscent of typical recurrent acute pancreatitis with "episodes of pain *lasting for days*, not minutes or hours" and "usually *aggravated by small amounts of food* so that the patients refuse all food by mouth. In the early stages, the bouts of pain are *severe* and are associated with *vomiting*." [23]. Some patients develop severe pain late in the course of the disease associated with an inflammatory mass in the head of the pancreas or other features. The characteristic of this type of pain is similar to B type pain described by Ammann et al [24] in alcoholic chronic pancreatitis, and remains resistant to all but the most aggressive treatment including major surgery.

Other contributors to this volume describe various clinical and pathological features of tropical pancreatitis in detail. However, it is clear that there remains marked variability in the presentation and clinical course of patients with pancreatic disease in Southern Asia. The clinical features and prognosis are further complicated by reports that are highly biased by referral patterns: the disorder looks very different in patients referred to the gastroenterologists for pain, the endocrinologists for diabetes, the surgeon for management of the most severe structural complications, or the pathologists who often only see the end-stage remnant of the pancreas. The clinical features and presentation of tropical pancreatitis has also changed over the past 50 years[3, 23, 25]. The consensus now is that the age of onset is older, the character is changing, but some aspects remain unique.

The most striking of these features, in comparison to the patients that are cared for by our group in the United States, is the strong propensity to diabetes mellitus – well before exocrine failure, and marked calcifications in a grossly dilated main pancreatic duct. It is also interesting to recognize that the severity of diabetes appears to correlate with the degree of calcification, suggesting that this represents a clearly different form of pancreatitis and that the pathophysicological mechanisms are linked.

Comparison of tropical pancreatitis and idiopathic chronic pancreatitis

A central question remains unanswered: Is the idiopathic pancreatitis seen in southern Asia only tropical pancreatitis, or is there a mixure of different disorders that have overlapping clinical features and pathologic appearances? As noted, this question remains unanswered. The primary reasons for this situation is that (a) there is no consensus on the distinguishing features of tropical pancreatitis, and (b) the molecular mechanisms have not been determined.

There are some mechanistic similarities between tropical pancreatitis in Southern Asia and idiopathic chronic pancreatitis in Europe and North America. In both cases a significant fraction of subjects have *SPINK1* mutations, and especially the N34S phenotype. Interestingly, this high-risk haplotype was only seen in a subset of children in Germany [18] or families in North America [19] with the phenotype of the heterozygous and homozygous being identical. [19] Since these mutations appear to lower the threshold for intrapancreatic trypsin activation, it appears that trypsin-related injury is a component of each of these disorders. Of even greater interest was the initial finding from Bangladesh in 2001 that *SPINK1* N34S mutations were associated with diabetes predominant tropical pancreatitis (fibrocalculous pancreatic diabetes, FCPD) and calcification/pain associated tropical pancreatitis (tropical calcific pancreatitis, TCP). [26,27] The association between the various forms of tropical pancreatitis was confirmed in India in 2002 by Chandak et al [28], and later by several other additional studies. [29-31] The biggest surprise was that there was a subset of patients with diabetes mellitus but without evidence of exocrine pancreatic disease that also had SPINK1 mutations in Bangladesh, a finding that does not appear in diabetes populations tested in the United States. [30]

It should be noted that there is a distinct phenotypic feature of FCPD in Bangladesh that clearly distinguishes it from diabetes caused by the destruction of pancreas in advanced chronic pancreatitis. Rossi et al demonstrated that compared to controls, patients having tropical pancreatitis and no diabetes showed normal plasma C-peptide values at baseline and after arginine stimulation, while FCPD demonstrated a

typical diabetic pattern for plasma C-peptide levels.[32] In contrast, pancreatic alpha-cell functioning was preserved in both pancreatitis groups.

The cystic fibrosis transmembrane conductance regulator, CFTR, plays a major role in the pathogenesis of pancreatitis in North America and Northern Europe. Initial studies from India suggest that in tropical pancreatitis, mutations in the CFTR gene are rare. However, it appears that both CFTR-associated chronic pancreatitis [14] and tropical pancreatitis are duct drainage problems. In CFTR-associated pancreatitis the problem is in generating proximal flow resulting in low head pressure. In tropical pancreatitis the primary problem appears to be in the main duct, where mucus (?) and large stones appear to cause distal resistance with high proximal pressures. This hypothesis is also supported by the observation that tropical pancreatitis, in some cases, is associated with pancreatic atrophy – similar to what is seen with other forms of pancreatitis duct obstruction. However, until the phenotype is clearly defined this hypothesis will remain theoretical.

Genes and environment

A number of environmental factors have been suggested to contribute to tropical pancreatitis. The most interesting is diet, including both protein and carbohydrate content, and consumption of cassava. Although a review of environmental factors associated with tropical pancreatitis is beyond the scope of this chapter, is should be remembered that the increased risk of tropical pancreatitis is of the order of 1.2 to 3 fold. Our studies in North America suggest that combined genetic factors confirm risk in the 200-500-fold range.[33] Thus the primary factor is genetic, while secondary factors are environmental. This is NOT to say that environmental factors are not important. For example, smoking cigarettes increases the risk of pancreatic cancer 1.5- to 2-fold. If the risk of population for pancreatic cancer is 0.8%, then 1.6% of smokers will generally get pancreatic cancer. However, in subjects with hereditary pancreatitis the risk of pancreatic cancer is about 50 times higher than the average risk of 0.8%[34] and about 40% of subjects will get pancreatic cancer. If smoking doubles this risk, then the impact of smoking is great.[35]. Knowing both the genetic and environmental risk

in the future will be important because the environmental risks are the easiest to change!

Taken together, it appears that the similarities between idiopathic chronic pancreatitis and TCP or FCPD are that the initial injury to the pancreas is trypsin-related. The difference is that the *response* to repeated injury differs between these groups. This hypothesis can be illustrated by considering Figure 2. In this case the third domain, the response to RAP that leads to fibrosis, could be replaced by other modifying factors that predispose to B-type pain, calcifications or diabetes (Table 1). Thus, all of the major features that define chronic pancreatitis are actually complications of RAP, with the most dominant features reflecting underlying genetic or environmental factors. This is a hypothesis that can be tested, and may further change the paradigm for understanding pancreatic disease.

Part 2 – Strategies to resolve complex genetic traits in India

The nation or the patient: What is the question?

As a physician who cares for individual people I want to know the problems that the *individual* patient faces, that threatens their health and well-being. At that moment I am less concerned with the percent of the population that has this or that disease; I want to know why this person is having symptoms, what underlying disorders are causing the specific symptoms, if they are at risk of developing additional problems, and how I can prescribe a special treatment or intervention that will address the symptoms and prevent any disease from progressing.

This approach is in sharp contrast to the questions and interest of allied health professionals. What they do is very important, and indeed essential to society. The epidemiologists are interested in factors that affect populations, the scientists are interested in the details of general biological principles and mechanisms, the pharmacologists are interested in agents that target specific biological pathways, the pharmaceutical companies want to provide effective agents to many people over many years, and the government is interested in the general well-being of the country, with special interest in public health initiatives that offer the greatest benefit to the most people for the lowest cost.

A special group is the physician-scientists in academic medicine. Their primary goal is to discover new knowledge about specific diseases, to integrate this knowledge into the correct context, and to communicate the insights gained from this new knowledge to all of the other interested health care-associated professionals, with special emphasis on training future physicians.

The *challenge* in academic medicine is to coordinate the varied interests of all of these parties so that there is efficient and effective cooperation among the different groups and that appropriate resources are made available to solve the major unknown questions that impact the patient. The strength of the leading academic physician-scientists is also their weakness – they are independent thinking and hold strong convictions based on their own ideas and interpretation. This is a critically important characteristic, because there can be no progress in medicine unless someone challenges the way medicine is currently practiced as being relatively ineffective, and proposing bold new approaches based on new insights developed by independent thinkers. The reason that the bold independence of the academic physician-scientists is a weakness is that they do not work well together as a group. The opportunity that physician-scientists recognize is that by investing a significant amount of their own time and effort into helping others with interest that are different than their own they can obtain critical data that is unique, important to their own interests, and cannot be otherwise obtain.

At this time, the primary question is: "How can pancreatic disease be prevented in individual patients that live in tropical and non-tropical regions of the countries in which we live?" The challenge will be to develop a consortium of interested parties that will provide sufficient support so that a committed core of focused physician-scientists can lead an effective working group to achieve a great thing that is otherwise impossible.

Planning to answer the major question about tropical pancreatitis

During the National Workshop on Tropical Pancreatitis a number of very important questions were raised. Some are epidemiological, and some are mechanistic. In planning a major study, multiple factors must be

considered and entered into the overall protocol or protocols so that at the end of the study, the major questions will be answered. I am most interested in complex genetic traits, and critical information needed to resolve disorders such as tropical pancreatitis should be obtained.

Complex trait genetics

On first glance, the challenges of resolving the interacting factors that make up a complex trait are daunting. There appears to be an infinite number of potential environmental factors and about a billion possible genetic mutations. However, the problem can be solved using insights from genetic linkage studies, epidemiology studies and systems biology (physiology).

Designing a study:

Several questions must be considered in designing a study. What is the question, what are the specific aims, what are the resources and (in the case of human studies) are there enough patients to answer the question if the specific aims are achieved? The problem of complex genetic traits compounds the difficulty in using power calculations to answer a question.

In the United States, as in Asia, it is becoming increasing clear that diseases of the pancreas result in a broad spectrum of clinical signs and symptoms. The variables include age of onset, presence or absence of acute attacks of inflammation, severity of attacks, degree of fibrosis, degree, nature and severity of pain, degree and location of calcifications, diabetes with or without insulin and/ or glucagon deficiency, and risk of pancreatic cancers. In addition, the exposure to metabolic or environmental risk factors (e.g. hormones, alcohol, tobacco smoking) appears to influence phenotypic expression.

Spectrum of pancreatic diseases in Southern Asia

The problem faced by investigators, including epidemiologists and geneticists, is that chronic pancreatitis is not a specific disorder, but rather a syndrome composed by multiple disorders with many *identical*

pathologic features, and not all individuals have all of the clinical features that are commonly seen in the disease. [36] Unfortunately, the current clinical "phenotype" is based on historical clinical criteria and has little to do with pathological mechanisms. Furthermore, if the phenotype is a syndrome, then it is by definition a group of signs and symptoms that tend to be seen together. In the case of inflammatory diseases of the pancreas, the syndrome is often based on pathologic features or abdominal imaging appearance.

The solution to this dilemma is to throw a broad net, to recruit ALL patients with any sign of recurrent acute or chronic pancreatitis. There should be minimal classification of patients into disease subtypes, especially if the phenotype is in doubt. Instead, there should be a very careful and comprehensive ascertainment of all of the signs and symptoms found in the individual patient, all of the laboratory and testing information, personal and family history, environmental exposures, and response to any therapies. In addition to collecting blood for DNA analysis, the radiographic images and pathologic specimens should be obtained. All of this information becomes critical as each feature of the complex trait is teased out of the overall disorder using a candidate gene approach. In addition, the same information should be obtained from a spouse or friend, and another family member so that the frequency of each candidate gene polymorphism can be compared with the frequency of the polymorphisms in a relevant population.

There also continues to be ongoing debate on exactly how many subjects are needed to have valid association studies[37]. Unfortunately, the current thinking is highly biased by epidemiological studies that require studies of over 1000 subjects in each group in order to have confidence that a variable with a small effect (e.g. OR 1.5) is truly associated with the phenotypic feature. In complex genetics that focuses on pathologic mechanisms, the primary genetic features will have combined effects with risk into the hundreds. The real issue in these studies is not *study size*, but *study power*, in which study size is considered as one component. However, since environmental features remain a very important consideration, large studies will be needed to clearly determine any association. Thus, from a molecular epidemiology and complex genetic trait perspective a study of 1000 subjects

and 1000-2000 controls will be needed. This could be accomplished within a couple of years if 20 dedicated centers each contributed 50 cases and appropriate controls, as we have demonstrated in the North American Pancreatitis Study 2 (NAPS2). Indeed, using much of the format and information of the NAPS2 study in an all-India study would be important for future comparison of subjects across the world.

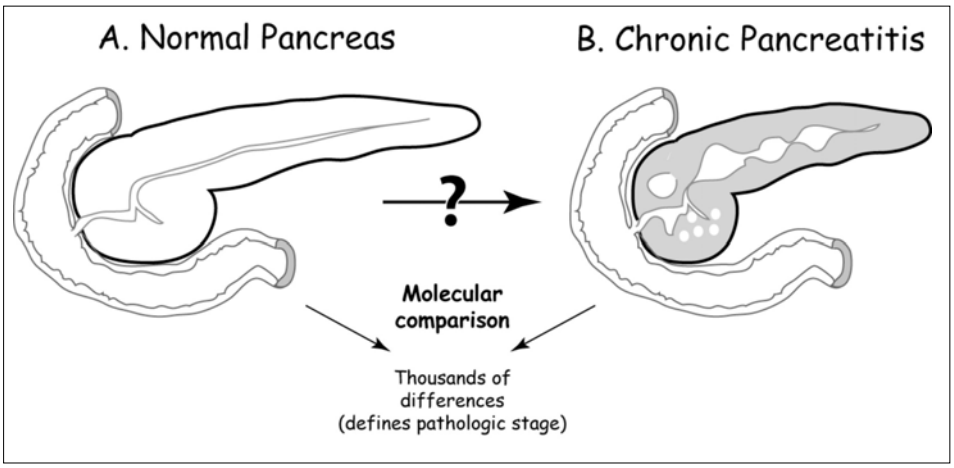

Figure 1: Comparison studies and etiology: Comparison of tissue form normal pancreas (A) with end stage chronic pancreatitis (B) is valuable for defining the histologic and pathologic features. Addition of molecular techniques provides information on thousands of differences between A and B. However, these approaches are more valuable in defining molecular pathology and staging than for determining etiology or prognosis. (From Whitcomb (13) with permission)

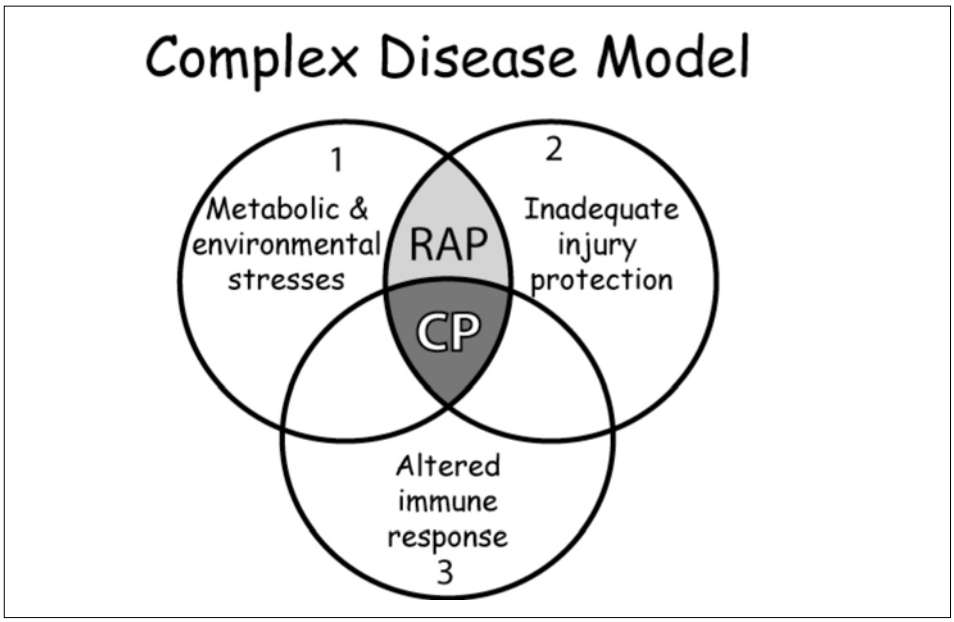

Figure 2: Three domains of chronic pancreatitis risk : Chronic pancreatitis is modeled as a complex trait in which one or more factors must be present in each of at least three domains before chronic pancreatitis develops. The three major genes with mutations that increase susceptibility to chronic pancreatitis (*PRSS1*, *SPINK1* and *CFTR*) are all in the domain of "inadequate injury protection" and lead to recurrent acute pancreatitis (RAP) in the presence of a sufficiently strong metabolic or environmental stressor. Only the subset of patients with an altered immune response favoring fibrosis develop chronic pancreatitis (CP), but this response requires RAP to direct it to the pancreas rather than other organs. (Modified from Whitcomb (13) with permission)

Table 1: Chronic pancreatitis as a complication of recurrent acute pancreatitis

(A) If the common underlying lesion in all cases of chronic pancreatitis is trypsin activation, then the spectrum of signs and symptoms of chronic pancreatitis could be considered as complication of recurrent acute pancreatitis, with the specific features reflecting underlying genetic and environmental modifying factors. (B) This could be the primary distinction between TCP and FCPD, in which both have SPINK1 mutations but different clinical profiles.

A) In patients with recurrent acute pancreatitis

- Normal response = healing
- Factor "A" Anti-inflammatory immune response = fibrosis
- Factor "B" = B-type - severe, continuous pain
- Factor "C" = Calcifications
- Factor "D" = Diabetes mellitus

B) Types of "tropical pancreatitis"

- RAP + A+B+**C** = tropical ***calcific*** pancreatitis (TCP)
- RAP + A+C+**D** = fibrocalulous pancreatic ***diabetes*** (FCPD)

References

1. Chiari H. Ueber selbstverdauung des menschlichen pankreas. Zeitschrift fur Heilkunde 1896;17:69-96.
2. Comfort M, Gambill D, Baggenstoss A. Chronic relapsing pancreatitis. Gastroenterology 1946;6:239-285.
3. Zuidema PJ. Calcification and cirrhosis of the pancreas in patients with deficient nutrition. Doc. Med. Geograph. Trop. Ansterdam 1955;5:229.
4. Sarles H. Pancreatitis: Symposium of Marseille, 1963. Basel: Karger; 1965.
5. Sarles H. Proposal adopted unanimously by the participants of the Symposium, Marseilles 1963. Bibliotheca Gastroenterologica 1965;7:7-8.
6. Sarles H, Adler G, Dani R, Frey C, Gullo L, Harada H, et al. The pancreatitis classification of Marseilles, Rome 1988. Scand J Gastroenterol 1989;24:641-641.

7. Sarner M, Cotton PB. Classification of pancreatitis. Gut 1984;25:756-759.

8. Sarner M, Cotton PB. Definitions of acute and chronic pancreatitis. Clinical Gastroenterology 1984;13:865.

9. Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg 1993;128(5):586-90.

10. Etemad B, Whitcomb DC. Chronic pancreatitis: Diagnosis, classification, and new genetic developments. Gastroenterology 2001;120:682-707.

11. Mack DR, Forstner GG, Wilschanski M, Freedman MH, Durie PR. Shwachman syndrome: exocrine pancreatic dysfunction and variable phenotypic expression. Gastroenterology 1996;111(6):1593-602.

12. Boocock GR, Morrison JA, Popovic M, Richards N, Ellis L, Durie PR, et al. Mutations in SBDS are associated with Shwachman-Diamond syndrome. Nat Genet 2003;33(1):97-101.

13. Whitcomb DC. Advances in understanding the mechanisms leading to chronic pancreatitis. Nat Clin Practice, Gastro Hepatol 2004;1(1):46-52.

14. Whitcomb DC. Value of genetic testing in management of pancreatitis. Gut 2004;53(11):1710-7.

15. Le Bodic L, Bignon JD, Raguenes O, Mercier B, Georgelin T, Schnee M, et al. The hereditary pancreatitis gene maps to long arm of chromosome 7. Human Molecular Genetics 1996;5(4):549-54.

16. Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Wong-Chong A, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110(6):1975-80.

17. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nature Genetics 1996;14(2):141-5.

18. 18.Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nature Genetics 2000;25(2):213-6.

19. Pfützer RH, Barmada MM, Brunskil APJ, Finch R, Hart PS, Neoptolemos J, et al. SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology 2000;119:615-623.

20. Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, et al. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. New England Journal of Medicine 1998;339(10):645-652.

21. Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. New England Journal of Medicine 1998;339(10):653-658.

22. Whitcomb DC. Hereditary Pancreatitis: New insights into acute and chronic pancreatitis. Gut 1999;45:317–322.

23. Pitchumoni CS, Mohan V. Pancreatitis: Juvenile Tropical Pancreatitis. In: Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR, editors. Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management. Hamilton (ON): BC: BC Decker; 2004. p. 1598-1605.

24. Ammann RW, Muellhaupt B, Group ZPS. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology 1999;116:1132-1140.

25. Mohan V, Premalatha G, Pitchumoni CS. Tropical chronic pancreatitis: an update. J Clin Gastroenterol 2003;36(4):337-46.

26. Rossi L, Pfützer RL, Parvin S, Ali L, Sattar S, Azad Kahn AK, et al. SPINK1/PSTI mutations are associated with tropical pancreatitis in Bangladesh: A preliminary report. Pancreatology 2001;1(3):242-245.

27. Pfutzer RH, Whitcomb DC. SPINK1 mutations are associated with multiple phenotypes. Pancreatology 2001;1(5):457-60.

28. Chandak GR, Idris MM, Reddy DN, Bhaskar S, Sriram PV, Singh L. Mutations in the pancreatic secretory trypsin inhibitor gene (PSTI/SPINK1) rather than the cationic trypsinogen gene (PRSS1) are significantly associated with tropical calcific pancreatitis. J Med Genet 2002;39(5):347-51.

29. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, et al. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. Gastroenterology 2002;123(4):1020-5.

30. Schneider A, Suman A, Rossi L, Barmada MM, Beglinger C, Parvin S, et al. SPINK1/PSTI mutations are associated with tropical pancreatitis and type II diabetes mellitus in Bangladesh. Gastroenterology 2002;123(4):1026-30.

31. Hassan Z, Mohan V, Ali L, Allotey R, Barakat K, Faruque MO, et al. SPINK1 is a susceptibility gene for fibrocalculous pancreatic diabetes in subjects from the Indian subcontinent. Am J Hum Genet 2002;71(4):964-8.

32. Rossi L, Parvin S, Hassan Z, Hildebrand P, Keller U, Ali L, et al. Diabetes mellitus in Tropical Chronic Pancreatitis Is Not Just a Secondary Type of Diabetes. Pancreatology 2004;4(5):461-467.

33. Schneider A, Barmada MM, Lamb J, Slivka A, money ME, Brand RE, et al. CFTR and SPINK1 mutations cause early onset idiopathic chronic pancreatitis. Nat Genet 2005;(in press).

34. Lowenfels A, Maisonneuve P, DiMagno E, Elitsur Y, Gates L, Perrault J, et al. Hereditary pancreatitis and the risk of pancreatic cancer. Journal of the National Cancer Institute 1997;89(6):442-446.

35. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. Journal of the American Medical Association 2001;286(2):169-170.

36. Tandon RK, Sato N, Garg PK. Consensus. Chronic pancreatitis: Asia-Pacific consensus report. J Gastroenterol Hepatol 2002;17:508-518.

37. Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: an empirical assessment. Lancet 2003;361(9357):567-71.

Chapter 2

Tropical pancreatitis - what is happening to it?

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Summary

Tropical pancreatitis is an entity first described in the 1950s. Though it was originally seen in young malnourished subjects from the tropics, this pattern is showing a gradual change. Older, better nourished patients are now affected by the disease. Alcoholism has increased in the population, and as a result, alcoholic pancreatitis too has gone up. Etiology of this disease is still not clear. The authors examine various hypotheses of etiology of TP and advocate the concept wherein pancreatitis of different types may have common etiological factors, but in differing proportions. The interplay of the environmental and genetic factors determine the phenotype of the disease.

Introduction

Tropical pancreatitis (TP) is a form of chronic pancreatitis of the young, originally described from the tropics. Though Zuidema had described malnourished young diabetics with fibrosis and calcifications of the pancreas in 1955[1] and again in 1959[2], and similar patients were described by Shaper[3] from Uganda, it was the report by Geevarghese[4] of a large series of young patients with malnutrition, diabetes and pancreatic calculi from Kerala state in South West India that focused attention on this condition, peculiar to developing countries.

When our group started work on tropical pancreatitis at the Medical College Hospital, Trivandrum, Kerala state in India in 1972, patients suffering from this disease were a common sight in our hospital, which was a referral centre, drawing patients from all the neighbouring districts. The tools that were available to us to investigate these patients were few. We had no ultrasound, CT scan, ERCP, MRCP or EUS. There were no pancreatic function tests being done in our hospital and genetic studies had not yet come of age. In short, we had to depend mainly upon the clinical picture, a plain X-ray of the abdomen, blood sugar estimations, biopsies from surgical specimens or an occasional autopsy to diagnose our patients. We started a registry for chronic pancreatitis and started recording details of our patients, and during the ensuing years, some of the newer investigational modalities became slowly available to us.

The clinical picture of tropical pancreatitis patients in those early years were so striking, that we could, most of the time, observe them walking around the wards, and make a "spot diagnosis". They were mostly children, adolescents, or sometimes young adults, who had the common characteristics of malnutrition, deficiency signs, a cyanotic hue of the lips, bilaterally enlarged parotid glands, a pot belly, and sometimes, pedal edema (Figure. 1)

This classical picture, with an elevated blood glucose level and the demonstration of a pancreas studded with dense intraductal calculi on X-ray abdomen would clinch the diagnosis. As far as diagnosis was concerned, there was no need for further investigations. However, there was a subgroup of these patients who did not show pancreatic calculi at the time of presentation, of whom many subsequently developed them. In the initial stages, in the absence of further functional studies or imaging modalities, diagnosis in this subgroup posed some difficulty. Our early patients were an almost equal mix of males and females, with a slight male preponderance. The distinctive feature of these patients were the near absence of any history of alcohol abuse, and mostly, smoking, thus contrasting them from the "alcoholic calcific pancreatitis (AP)" of the West. They had no gallstones or other detectable causes of pancreatitis.

Ketosis occurred in 15% in our early series[5]. They had high blood sugar values, often in the ranges of 200-400 mg/dl, requiring generally, large doses of insulin for control, had a brittle diabetes, and were frequented by episodes of hypoglycemia. During the sixties and seventies, a number of reports started coming in from other Asian and African countries[6, 7, 8], and even from Brazil[9] in South America, describing similar young malnourished diabetics with pancreatic calculi. The common denominator of the countries afflicted by this malady was their location in the tropics, poverty and poor standards of nutrition. Large segments of population in such countries also regularly consumed cassava (tapioca), a tuber containing starch almost exclusively, with negligible quantities of protein (and amino-acids) as their staple diet. This close association with tropics, poverty and malnutrition earned the disease synonyms such as "Nutritional pancreatitis", "Afro-Asian pancreatitis", "Juvenile pancreatitis", and "Tropical pancreatitis". At that time, these descriptive terms were useful to segregate such patients from the well-

recognized entity of "alcoholic pancreatitis". This geographically descriptive term was also a reflection of the ignorance about the etiology or etiologies of this newly recognized disease. In the seventies and early eighties, we seldom saw patients of alcoholic chronic pancreatitis in our hospital. The following are results of studies in our early series (in the seventies and eighties) of nearly 250 patients with TP.

Clinical details

The male to female ratio in our patients was 1.6 :1. The mean age of presentation of the disease was 30.5 years in the calcific group and 22 years in the noncalcific group.[5] This might indicate that calcification is a function of time. The clinical features of our patients are given in Table 1.

Pain was the commonest presenting symptom, closely followed by diabetes mellitus.

Table 1. Demographic and clinical features

	Calcific n=155	**Non-calcific n=65**
Age (mean) at presentation	30.5 (years)	22 (years)
M:F	2.7:1	1:1
Pain	84%	80%
Duration of pain	7.9 (years)	3.6 (years)
Diabetes	76%	81%
Duration of diabetes	6.0 (years)	4.8 (years)
Complications of diabetes	27%	46%
Steatorrhoea	72%	81%
Surgery	25%	15%

Retinopathy, peripheral neuropathy and nephropathy were common complications of diabetes[10]. (Table 2)

Table 2. Tropical pancreatic diabetes - complications

Complications	Percentage
Ketosis	15
Hypoglycemic episodes	20
K.W. Syndrome	10
Neuropathy	69
Retinopathy	34
Tuberculosis	5

Most patients of tropical pancreatitis died in their thirties as a result of nephropathy or infections. Many of them developed pulmonary tuberculosis. Some of our patients (10%) developed malignancy of the pancreas on follow up and succumbed to it. Nearly twenty five percent of patients with tropical pancreatitis in this series had to undergo surgery – mostly for intractable pain, occasionally for proven or suspected malignancy, pseudocysts or common bile duct obstruction.

In the early surgeries, there was no standardization of the surgical procedures and based on the operating surgeon's judgement, various procedures such as sphincterotomy or sphincteroplasty, often combined with scooping out of stones from an opened main pancreatic duct, drainage procedures, resections and splanchnicectomy were all employed.

Surgery

Out of a series of 64 patients operated upon, 47 had the surgery done for severe intractable pain. Nine had carcinoma pancreas complicating TP, 10 had obstructive jaundice (6 having associated carcinoma), 5 had pseudocysts and 2 pancreatic ascites. Eighty-six percent of patients had immediate pain relief and 68% remained pain free on follow up of up to 5 years[5].

Diet

In a collaborative study with Prof. Sarles from Marseille, France, we compared the diets between South Indian (TP) and French (AP) chronic pancreatitis patients, and matched South Indian and French controls[11]. We noted that the French patients consumed a high calorie, high fat, high protein diet, whereas the South Indian patients and controls consumed a high carbohydrate, low protein and very low fat diet. (Table 3). The latter also consumed 370 g/day of cassava in their diet.

Table 3. Comparison of diet of Indian and French patients and controls

	Indian CCP	**French CCP**
Calories	1966.1 ± 154.8	3411.0
Proteins (g/day)	55.7 ± 5.8	123.8 ± 56.4
Fat (g/day)	23.4 ± 2.8	122.6 ± 50.4
Carbohydrate (g/day)	354.2 ± 22.4	452.5 ± 178

	Indian Controls	**French Controls**
Calories	2012.9 ± 173.6	2453.0
Proteins (g/day)	51.3 ± 4.9	94.8 ± 29.5
Fat (g/day)	25.5 ± 3.4	96.9 ± 28.8
Carbohydrate (g/day)	385.7 ± 37.2	300.3 ± 104.4

Exocrine functions

Clinical steatorrhoea was not very common in our patients (10%). However, 75% of them showed biochemical steatorrhoea when administered a high fat (100 g butter supplements) diet. The mean stool fat excretion by Van de Kamer estimation was 21.3 g in 24 hours[12].

In a separate study of 30 patients with TP and 10 healthy controls we estimated the faecal fat and meal stimulated tryptic activity in the duodenal aspirate[13]. The mean ± SD tryptic activity (MTA) was 19.6 ± 3.51 µEQ /min/ml in controls, 6.2 ± 3.91 µEQ /min/ml in patients with

noncalcific pancreatitis and 2.75 ± 2.92 μEQ /min/ml in those with calcific pancreatitis. Ninety percent of the TP patients showed subnormal (less than12.4 μEQ /min/ml duodenal tryptic activity and steatorrhoea. No correlation was found between the severity of steatorrhoea and the level of tryptic activity.

In a collaborative study with the group from Marseille[11], the exocrine pancreatic function after secretin-CCK stimulation was assessed in South Indian TP patients and French AP patients and matched South Indian and French controls. (Table 4).

Table 4. Comparison of biochemical parameters in pancreatic juice of South Indian (TP) and controls French patients (AP) and controls

	Indian CCP	A	TP	B	AP	Controls	C	D
Bicarbonate (mEq/L)	23.4 ± 4.4	S	60.4 ± 4.6		71.6 ± 4.8	40.8 ± 4.1	S	S
Calcium (mEq/L)	3.7 ± 0.3	S	3.2 ± 0.5	S	1.9 ± 0.2	2.4 ± 0.2	S	S
Amylase (Ul/ml)	100.0 ± 35.4	S	205.2 ± 31.6		398.7 ± 94.3	241.4 ± 34.6	S	S
Lipase (Ul/ml)	102.1 ± 34.9	S	957.0 ± 109.0		1089.3 ± 82.6	469.6 ± 76.2	S	S
Phospholipase (Ul/ml)	1.8 ± 0.8	S	9.1 ± 1.2	S	21.4 ± 2.6	10.5 ± 2.4	S	S
Trypsin (Ul/mL)	2.9 ± 0.9	S	19.2 ± 1.9		25.6 ± 1.4	7.7 ± 0.9	S	S
Chymotrypin (Ul/mL)	22.6 ± 8.4	S	118.1 ± 7.8	S	149.0 ± 11.5	73.7 ± 10.2	S	S
Lactoferrin (ug/mL)	19.4 ± 8.9	S	1.7 ± 1.6		0.1 ± 0.07	4.8 ± 2.3	S	S

Displayed values are mean ± SEM
A. Indian CCP vs. Indian controls ($p<0.05$); B. Indian controls vs. French controls ($p<0.05$);
C. Indian CCP vs. French CCP ($p<0.05$); D. Indian CCP vs. French controls ($p<0.05$)
S=significant

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We observed that the South Indian patients with TP had very low lipase and phospholipase levels in their pancreatic juice compared to French patients. Further, even the Indian controls exhibited markedly reduced enzyme secretions than their French counterparts. However, the calcium and lactoferrin levels, which have been thought to indicate pancreatic injury, were significantly higher in the Indian controls than in the French controls.

From these studies, we proposed that perhaps, among the malnourished population in the tropics, there existed a condition of "subclinical pancreatopathy"[11] that became overt when a second insult to the pancreas supervened.

Family studies

We did HLA studies in members of seven families with more than one patient of TP in each. Six of the seven families and eight of twelve patients shared the HLA AW19/AW10 haplotypes, suggesting a possible genetic role in the causation of this disease[14]. In a subgroup study, in the family members of 24 patients with calcific pancreatitis, there were 12 family members with TP, 16 with type 2 diabetes, and 1 with pancreatic cancer[5]. In the families of 15 patients with non-calcific pancreatitis, there were 3 members with pancreatic calculi, including a twin sister, 11 with type 2 diabetes and 1 with carcinoma pancreas. These findings pointed to a strong family background common to TP, type 2 diabetes mellitus and carcinoma pancreas, and possibly, a genetic predisposition.

Infection

In another study, we tested for antibodies against rubella, mumps, CMV and M-pneumoniae in the sera of patients with TP and controls and found that significantly more numbers of patients were tested positive for antibodies against mumps and CMV than the controls; however, in the case of M. pneumoniae, more controls than patients were tested positive[15] (Table 5).

Table 5. Viral and M. pneumoniae antibodies in chronic pancreatitis

Agent		Total no. tested	No.+ve	Antibody titre		Chi square	P value
				<1:32	>1:32		
Rubella	Patients	51	41	1	40	-	-
	Controls	60	50	0	50	-	-
Mumps	Patients	52	46	21	25	19.07	<0.001
	Controls	45	44	40	4		
CMV	Patients	39	36	14	22	15.57	<0.001
	Controls	45	33	29	4		
M.pneumoniae	Patients	52	26	14	12	12.02	<0.001
	Controls	45	42	5	37		

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In the above study seriological evidence of current viral infection was present in 12 of our patients with chronic pancreatitis (4 with rubella, 2 with CMV, 4 with mumps and 3 with M.pneumoniae) as evidenced by a four to eight fold rise in antibody titres.

In yet another study, 66.7% of our TP patients showed coxsackie B antibodies in their serum[16]. Injection of extracts of pancreatic tissue and pure pancreatic juice, obtained during surgery, into suckling mice, did not yield any viral agents, nor did it produce any pancreatic lesions.

Immunity

Sera from 60 of our patients with TP and 20 normal controls were tested against a pancreatic antigen prepared in our laboratory for antipancreatic antibodies by a hemagglutination test. Sixtynine of the patients (29%) tested positive for the antibodies against the pancreatic antigen, but none of the controls. We also failed to detect any autoantibodies in the sera of our patients on testing for a panel of autoantibodies[17], apart from 6 patients tested weakly positive for parietal cell antibodies and one weakly positive for islet cell antibodies (Table 6)

Table 6. Anti-pancreatic and auto immune antibodies and C3 in tropical pancreatitis patients

Antibodies & Complement	Patients		Controls	
	No. tested	Positive	No. tested	Positive
Anti-Pancreatic Antibodies				
positive titre of >1/8 (Indirect hemagglutination test)	69	20	30	Nil
Autoantibodies				
Antinuclear	12	Negative	10	Negative
Smooth muscle	12	Negative	10	Negative
Antimitochondrial	11	Negative	10	Negative
Islet cell	11	Negative	10	1 weakly +ve
Parietal cell	24	6 weakly +ve	10	Negative
Thyroglobulin haemaggluttinating	11	Negative	10	Negative
Adrenal	11	Negative	10	Negative
C3	11	Negative	10	Negative

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ERCP

ERCP findings in TP were reported for the first time by our group in 1985[18]. The ERCPs showed marked tortuosity, dilatation, stenosis, obstruction and cyst formation in the main pancreatic duct and finer branches with multiple large intraductal calculi and the findings were similar to, but more pronounced, than those described in alcoholic pancreatitis (Figure 2).

Calculi, protein plugs

In a study of pancreatic calculi from patients with TP, the stones were found to vary in size from large to small, were whitish or dirty brown, gritty or thorny, and adherent to the duct walls and were always intraductal. The stones were analyzed by scanning electron microscopy, atomic absorption spectrophotometry, chemical analysis, thermo-analytical methods, infrared spectrometry and X-ray diffraction. The chief constituent of the stones was found to be calcium carbonate, constituting 95 to 98 percent[5]. Crystallographic studies using X-ray diffraction revealed that the calcium carbonate existed as calcite.

Scanning electron microscopy revealed the presence of amorphous and crystalline material in the stones[19]. The crystals were of a rectangular form and were heaped one upon the other. Interlacing fibres of 3-5 microns were seen in between the deposits. These findings bear resemblance to that of one of two types of stones described by Harada in AP from Japan[20] (Fig 3).

Pure pancreatic juice and protein plugs from pancreatic duct collected during ERCP were studied under the electron-microscope and scanning electron microscope. Clumps of amorphous material deposited in the spaces between interlacing fibres were observed. There were deposits of varying sizes on the surface of the clumps as well as on the fibres. These protein plugs appear to form the nidus for deposition of calcium on and within its meshes with subsequent stone formation (Fig 4).

Chemical composition of pancreatic calculi was studied using atomic absorption spectrophotometry (Table 7).

Table 7. Trace elements in calculi from TP

Element	Mean ± S.E. Mg/g dry weight
Calcium	379.4 ± 0.8365
Copper	0.0256 ± 0.0096
Magnesium	0.0176 ± 0.0033
Cadmium	0.0058 ± 0.0011
Iron	0.0306 ± 0.0087
Manganese	0.0072 ± 0.0006
Zinc	0.1552 ± 0.0485
Cobalt	0.023 ± 0.0007
Aluminium	0.0728 ± 0.0044

The changing pattern of TP

The first author of this article has been actively involved in the care of patients and study and research in pancreatitis, and particularly on chronic pancreatitis of the tropics over a period of three decades. He has personally treated, recorded and followed up more than a thousand patients with tropical pancreatitis and has been a keen observer of the changing trends in the epidemiology and clinical course of this disease. These observations have brought to his attention several social, dietary and life-style changes that have occurred during the past thirty and odd years in Kerala state, where the highest prevalence of tropical pancreatitis has been recorded in the world, which could have influenced, to a great extent, the changing trends in the natural history and occurrence of the disease in the state[19]. It will be interesting to examine what these socioeconomic and lifestyle changes are and how these could have influenced the clinical presentation of this disease.

Firstly, people are more literate now (nearly 100%) and the standard of living has greatly improved[21]. There is better hygiene, as a result of better literacy and health awareness and standard of living. Cassava, which was an inexpensive poor man's diet, has been replaced to a large extent, by rice, through improved purchasing power and availability through

the public distribution system[22]. People eat more fish, meat and poultry. Medical facilities have remarkably improved and are more easily accessible than what obtained thirty years back. Diabetics are better cared for and more closely monitored, thanks to a parallel, or even more powerful network of private healthcare facilities. There are large numbers of specialists available in the all regions of the state, which is like an extended township. Early detection of diseases has become common. Facilities such as ultrasound and CT scan are now readily accessed, and even ERCP, MRCP and EUS are now available in the larger centres. The longevity in the state has risen dramatically, boasting of the country's best figures[21]. Along with this, on the negative side, alcoholism has become extremely common, and according to recent figures, Kerala's per head annual consumption of liquor is thrice that of the national average[23]. Smoking is rampant. Pollution from factories, exhaust from motor vehicles, toxins from pesticides and adulteration of foodstuffs have phenomenally increased. Genetic studies are now available in a few major centres in the country and patterns of genetic mutations in diseases are being reported, particularly so in pancreatitis. In a vast country like India, geographical variations in the genetic make-up are expected. It is but natural that such social, dietary, life-style, and environmental changes, on a genetic background (that has many commonalities, but at the same time, with variety thanks to the size and heterogeneity of the population) would influence the pattern of several diseases. Perhaps, in the case of tropical pancreatitis, this is what must have been happening. The occurrence and extent of such influences, and the combination of factors that has wielded such influences, are still matters of speculation.

Study of a new cohort

In the light of the above observations, we compared a cohort of about 250 patients with chronic pancreatitis that we have prospectively followed up during the past 5 years to a cohort of 250 patients of chronic pancreatitis that was studied and followed up by the first author personally during the seventies and eighties, that is, 30 to 20 years earlier. Such comparison should be interesting and educative.

The current cohort of nearly 250 patients with chronic pancreatitis were seen and followed up by us at the Amrita Institute of Medical Sciences, Cochin, in Kerala state in India during the last 5 years. In our current series of 255 patients, 226 have chronic pancreatitis and 29 have recurrent acute pancreatitis. Pancreatic calculi were present in 213 of the chronic group and 13 were without calculi. Of the 29 patients with recurrent acute pancreatitis, 18 developed calcification during follow-up and they were included in the chronic pancreatitis group for the present analysis. Of these 18 patients, 11 were alcoholic and the rest gave no history of alcohol.

Among the non-alcoholic patients in our current cohort, 2 have hypertriglyceridemia and one hyperparathyroidism. Four patients have pancreas divisum. Eight patients have associated cirrhosis of the liver, of whom 7 are among the alcoholics. The demographic and clinical details of these patients are given in Table 8.

Table 8. Demographic and clinical details of new cohort of patients

Variables	Whole group of 244 patients	
	No.	%
Gender		
Male	170	69.6
Female	74	30.3
Socio-economic status		
Poor	34	15
Lower middle	116	51.1
Upper middle	72	31.7
Rich	05	2.2
Clinical features		
BMI		
18-25	70	69.3
<18	25	24.7
>25	5	4.9
Age of presentation	39.1 ± 12.87	
Age of onset of Pain	30.8 ± 14.56	
Age of onset of DM	36.2 ± 11.27	
Pain (**n** = 243)	233	95.9
Steatorrhea (**n** = 203)	94	38.4
Diabetes (**n** = 243)	145	59.7
Calcification	231	94.7
Duct dilatation (**n** = 225)	196	80.4
No. of alcoholics **n**=158 males	77	33.2 (among whole) or 48.7 among males
No. of smokers (**n** = 221)	75	33.9
Family history		
Diabetes (**n**=173)	87	50.2
Pancreatitis (**n**=158)	19	12
Ca pancreas	12	4

where **n** is the number of patients whose data is available

The majority of patients (70%) had a BMI within the normal range (mean 20.4; range 14.03 – 27.85), as compared to the BMI of 15.9; (range 9.6 – 21.07) of our cohort of 1984. Thus the majority of patients in the current series were moderately to well-nourished.

The predominant symptom is pain, which occurred in 95%. Nearly 60% of the patients are diabetics. Thirty eight percent of them have clinical steatorrhoea.

The age of onset of disease, and the ages of presentation and duration of the main symptoms are given in table. It will be noticed that the age of presentation is more than one decade later than in the earlier series (Fig 5).

Forty nine percent of our male chronic pancreatitis patients consume alcohol. Of the whole group, including males and females, 33% are patients with alcoholic pancreatitis. For this study, we applied a threshold level of 80g of alcohol intake daily for 5 years. As opposed to our earlier series where 98% of patients (except 2 percent of alcoholic pancreatitis) had tropical pancreatitis, in the current series, nearly one third of our total number of patients, and nearly half of the male patients are suffering from alcoholic pancreatitis. In addition, 17 patients among the 'non-alcoholic' group are occasional or 'social' drinkers. This shows that alcoholic pancreatitis is on the rise in this state where we used to see earlier, almost exclusively, tropical pancreatitis. It is also possible that alcohol, in smaller amounts, as in the social drinkers, might be having an additive role, along with other dietary or environmental toxic factors, even in the causation of "idiopathic" or "tropical pancreatitis", as there is no real cut-off value for the harmful effects of alcohol[24].

Forty percent of the patients are smokers, and it was interesting to observe that 83 percent of the alcoholics were also smokers. The combined effect of alcohol and tobacco are known to contribute to the development of chronic pancreatitis[25], and even pancreatic cancer[26].

We compared the features of our alcoholic with the non-alcoholic group of patients. In the alcoholic patients, the age of onset and the age of presentation of the disease are both about a decade later than in the non-alcoholic group (Table 9).

Table 9. Comparison of age of onset and age of presentation between alcoholics and non-alcoholics

	Alcoholics	Non-alcoholics	p value
Age of presentation	45.4 ± 9.71	35.9 ± 2.92	0.000
Age of onset of pain	36.1 ± 13.49	27.4 ± 13.94	0.000
Age of onset of DM	41.53 ± 9.56	32.6 ± 10.4	0.000

The age of onset and presentation in the alcoholics are more or less same as those of alcoholic pancreatitis described in other reports. The nonalcoholic group is a mix of classical cases of tropical pancreatitis and idiopathic pancreatitis, which explains this age difference between the alcoholic and the nonalcoholic groups. We are also looking at any possible genetic differences between the alcoholic and the nonalcoholic pancreatitis groups.

Sixty percent of the patients are diabetics. The mean age of onset of diabetes is 36 years. The age of onset of pain and the age of presentation are about 7 years and 9 years later, respectively, in the diabetics as compared to the non-diabetic group, which is significant (Table 10). This raises the question whether TP and FCPD are two different diseases. However, this issue is still contentious and awaits further proof. It is also possible that these two conditions may be different expressions of the same disease.

Table 10. Comparison of age of onset and age of presentation between diabetes and non-diabetes groups

	Diabetes	Non-diabetes	p value
Age of presentation	40.54 ± 11.747	28.26 ± 10.68	0.000
Age of onset of pain	29.47 ± 15.16	20.77 ± 10.98	0.000

The diabetic patients had significantly more clinical steatorrhoea (47.2%) than the non-diabetics (24.4%; p 0.001). However, there is no correlation between diabetes, and pain, calcification or ductal dilatation (Table 11)

Table 11. Correlation between diabetes, pain, steatorrhea, calcification or ductal dilatation

		Diabetes		Non-diabetes		p value
		No.	%	No.	%	
No. of patients		145	59.7	98	40.3	
Pain	Yes	137	94.5	96	98	0.157
	No	8	5.5	2	2	
Steatorrhoea	Yes	59	47.2	19	24.4	0.001
	No	66	52.8	59	75.6	
Calcification	Yes	140	96.6	90	91.8	0.096
	No	5	3.4	8	8.2	
Duct dilatation	Yes	106	81.5	75	78.9	0.375
	No	24	18.5	20	21.1	

We searched for possible correlations between pain, and ductal dilatation, calcification or diabetes, but there was no correlation (Table 12).

Table 12. Correlation between pain, and ductal dilatation, calcification or diabetes

		Pain				
		Yes		No pain		
		No	%	No.	%	p value
Ductal dilatation	Yes	172	79.6	9	100	0.136
	No	44	20.4			
Calcification	Yes	220	94.4	10	100	0.571
	No	13	5.6			
Diabetes	Yes	137	58.8	08	80	0.157
	No	96	41.2	02	20	

Table 13 looks at correlations between ductal dilatation and pain, calcification or steatorrhoea. There was positive correlation between ductal dilatation and calcification.

Table 13. Correlation between ductal dilatation, and pain, calcification or steatorrhoea

		Ductal dilatation				p value
		Yes		No		
		No.	%	No.	%	
Pain	Yes	172	95	44	100	0.136
	No	9	5			
Calcification	Yes	174	96	38	86.4	0.02
	No	7	4	6	13.6	
Steatorrhoea	Yes	56	36.6	15	41.7	0.351
	No	97	63.4	21	58.3	

Nearly 50% of the patients consumed cassava in significant quantities. However, the mean daily intake of cassava was 171.8 SD 170.8g/day, which is much lower than the intake in our earlier cohort (370 g/day). This is because cassava has, to a large extent, been replaced by rice as the staple diet even among the poor in the state. The age of presentation, onset of pain and onset of diabetes mellitus were also about 3-4 years later in the cassava eaters than in the cassava non-eaters. However, these differences were not statistically significant.

There were 12 patients who developed malignancy in our current series of chronic pancreatitis. Apart from this, there were 9 cases of carcinoma pancreas complicating TP who directly attended the G.I. Surgery clinic. They are not included in this analysis of TP cases.

Our observations

What are our important observations on the changes that have occurred in tropical pancreatitis over the past 2- 3 decades? Firstly, the age of onset of the disease and the age of presentation have shifted to the right by a decade[27]. The patients in the current series are better nourished than those in the earlier series. Malnutrition is now much less common. The diabetes mellitus is milder and is better controlled, often with diet and oral hypoglycemic drugs alone. The patients with TP eat less cassava now than their predecessors and, in addition, newer varieties of cassava with reduced cyanogenic content are available now. Alcoholism has

phenomenally increased in India in general, and in Kerala in particular, and as a result, we see many more cases of alcoholic pancreatitis now than earlier. A large number of the alcoholics are smokers too and there is the likelihood of an additive effect of smoking with alcoholism in the causation of pancreatitis. Patients of chronic pancreatitis live longer (many of them to fifties and a few, even to sixties), and fewer require surgery for relief of pain, as in a large number, pain can be controlled with medical treatment. However, because of increased longevity, and perhaps, as the effect of environmental and genetic factors, our patients develop malignancy more frequently. In our experience, the incidence of chronic pancreatitis has not come down in the state, but we feel that this impression is consequent on a comparative reduction in the number of the classical cases of "tropical pancreatitis" that we used to see earlier. There are now small series of cases reported from other parts of India, particularly Northern India, of "tropical pancreatitis" occurring in these regions[28,29] Whether these cases truly conform to the "classical" features of "tropical pancreatitis", or they are simply "idiopathic pancreatitis" is a matter of speculation. It is noteworthy that almost all these populations are cassava non-eaters. If the cases of TP described from Northern India are true cases of TP, then it is an argument against cassava being a major etiological factor in TP. However, it has to be admitted that even in the heartland of tropical pancreatitis, Kerala, the classical picture of tropical pancreatitis is gradually fading and merging with the picture of idiopathic pancreatitis.

What causes tropical pancreatitis?

Now, we come to the important question, what causes tropical pancreatitis? We have to admit that, as of today, we do not know the exact cause/causes. The hypothesis that protein deficiency is the cause of TP held sway over a long period [30]. Even though this is an attractive proposition, concrete proof is lacking to implicate protein deficiency as the sole, or even the major cause of TP[31]. The high carbohydrate content of cassava and its low protein value, together with its cyanogen content made the cassava hypothesis look a plausible one. Moreover, the close geographic association between cassava consumption and the prevalence of TP in many tropical countries support this hypothesis[32]. In dietary studies conducted by us in our earlier cohort of patients with

TP and age and sex matched controls from the same geographical region, the cassava intake did not show significant differences between the two groups (370 g/day Vs 309 g/day)[10]. Moreover, as mentioned earlier, TP is now reported from many parts of India where cassava is not consumed at all [28,29]. Cyanogenic glycosides are tissue toxins, and it has been suggested that certain other foodstuffs consumed in these regions of India contain cyanogenic glycosides, or other similar tissue toxins. Tuescher and colleagues have also reported the absence of diabetes mellitus in rural West African population whose diet predominantly consisted of high starch cassava[33]. Environmental toxins or pollutants also deserve attention as co-factors in the etiology. In fact, Braganza had proposed the "oxidant stress" theory of pancreatitis[34]. According to this theory, the toxic effects of oxygen derived free radicals and lipoperoxidases can cause pancreatic damage. Exposure to xenobiotics, induction of detoxifying mixed function oxidases, and excess production of unmitigated metabolites and free radicals have been proposed to cause damage to cellular membranes. An imbalance between these toxic substances and antioxidants could lead to pancreatic injury. Deficiency of antioxidants such as vitamins A, C and E has been demonstrated in chronic pancreatitis[35]. Alcohol itself has been shown to contribute to oxidant stress.

The observation by our pathologists that the pathological changes in the acini in TP are primarily an atrophy and that inflammatory changes are minimal, lend credence to a dietary etiology[36]. Sandhyamani, from her observations on autopsy of patients with endomyocardial fibrosis and also from feeding experiments in bonnet monkeys described deposition of mucopolysacharides (proteoglycans) in the walls of blood vessels and connective tissue and sclerotic changes in the blood vessels in different organs including the pancreas. She has dubbed these changes as a "mucoid vasculopathy"[37,38]. She attributes these changes to a dietary imbalance, or to be more precise, a high carbohydrate, low protein diet fed to her experimental monkeys. These changes were noticed irrespective of whether the source of the carbohydrate was cassava or corn starch. The findings in the pancreas in her autopsies in humans and in the experimental monkeys closely resemble the early changes in TP. It is noteworthy that in alcoholic pancreatitis in France, Sarles and colleagues observed that a high fat, high protein diet, and

next, a very low fat diet also, predisposed his patients to alcoholic pancreatitis[24]. This also points to dietary imbalances as a cause for pancreatic damage. In our studies with the French group, we have recorded a high carbohydrate, low protein and very low fat diet in our patients from South India with TP[11,39]. We had recorded our suspicion whether the low fat content in our TP patients would have made them more susceptible to develop pancreatitis. We also reported low pancreatic enzyme levels and high calcium and lactoferrin content in the pancreatic juice of even our normal controls and proposed the entity of a "subclinical pancreatopathy" in populations where the diets are not necessarily "inadequate", but are "unbalanced"[11]. Such a subnormally functioning pancreas (with most likely, early structural changes too) must be prone to injury when another injurious agent/ agents or insult supervenes. Even though there is no evidence so far that cassava could be a sole etiological agent for pancreatitis, its role as a cofactor (due to its cyanogen content) cannot be entirely ruled out. The fact that the poor and low middle class population of Kerala now eat lesser quantities of cassava than their predecessors and that the varieties that are cultivated and consumed now are less toxic ones could mean a lesser exposure to the cyanogen content than would have been the case earlier. This might partially explain the later age of onset of the disease now. In addition, there are cofactors now that were not significant a couple of decades earlier.

These cofactors could be consumption of moderate quantities of alcohol, smoking, environmental toxins or pollutants, oxidant stress or even an infection. As has been demonstrated in the case of the liver that even moderate alcohol consumption promotes oxidative stress in chronic hepatitis C (CHC) patients, suggesting a role for oxidative injury in the worsening of CHC evolution by alcohol[40,] the pancreas also might be vulnerable to oxidant stress from moderate quantitities of alcohol. These environmental stresses may be abetted and modified or facilitated by one or more mutations in genes such as SPINK 1, PRSS1, CFTR, or even some novel gene mutations as have been demonstrated[41,42,43,44].

The nature of the exposure to such combinations of injurious agents or factors, and the genetic make up of the individual, determine the type of pancreatitis one develops and also the phenotype. At one end of

this spectrum is the classical alcoholic pancreatitis; at the other, the classical tropical pancreatitis. In between these two, there could be a spectrum of a variety of manifestations of the disease depending on the combination of environmental stress and genetic make up. Thus, the etiology of chronic pancreatitis in general, and tropical pancreatitis in particular, we believe, is complex and multifactorial and may involve more than one environmental factor and may be modulated by polygenic influences. Alcohol, in doses less than that generally recognized to cause alcoholic pancreatitis, and varying degrees of smoking, may also add up as injurious agents, as seen in our intermediate group of so-called "social drinkers". In addition, the change in lifestyle that have occurred over the years in our state have resulted in a sizeable proportion of our chronic pancreatitis patients conforming to the definition of alcoholic pancreatitis. It should be noted that the majority of the alcoholics were smokers too.

A novel concept

Tropical pancreatitis is likely to be multifactorial, as the first author had observed 20 years ago[45], and perhaps, this is true for many other types of chronic pancreatitis. We believe, therefore, that the old sharp compartmentalization of alcoholic and tropical pancreatitis as two separate entities, poles apart, is now becoming slowly blurred. In alcoholic pancreatitis, even though alcohol is a predominant etiological factor, there are other possible co-factors such as smoking and diet (high fat, high protein diet) and genetic factors that contribute to hasten the onset of the disease process.

In the same way, in TP too the dietary imbalances (high carbohydrate high protein diet, low fat diet) and/or toxins in diet or atmospheric pollutants (xenobiotics), along with moderate amounts of alcohol and smoking and possible genetic influences are likely to be contributory to the pancreatic damage. Free radical stress should be a common factor for both TP and AP, though the causes may be different. We consider that in the case of TP, injurious agents such as alcohol, smoking dietary toxins, atmospheric pollutants and the resultant oxygen stress must be acting as the "second hit" on a pancreas that is already suboptimally functioning as a result of a "subclinical pancreatopathy". Both these

conditions (AP and TP) are two ends of a spectrum with a complex interplay of multiple injurious factors filling the gap between these extremes. And this intermediate region is represented by many patients in our current series of "tropical pancreatitis", which no more resembles the classical TP of old, but occurs in a more varied form in the not so young, fairly well-nourished, and occasionally alcoholic or smoking population whose diets may be unbalanced, who are exposed to a number of atmospheric or food toxins and who have varied genetic mutations or polymorphisms that make them prone to be victims of injury to their pancreas. Another region of this spectrum is occupied by the "idiopathic" type of pancreatitis. Thus, tropical pancreatitis is now moving closer to "idiopathic" pancreatitis, and the distinction between "idiopathic" and "tropical pancreatitis" is slowly fading and we are left fumbling to find new definitions for this enigmatic disease we now call "TP". This new paradigm compels us to shift our focus from searching for exclusive etiological factors for a chronic disease such as chronic pancreatitis, to a more broad and comprehensive understanding of a wide range of environmental toxins, dietary factors, environmental stresses, infections and genetic polymorphisms or mutations involving multiple genes, and also alterations in our genetic competence in handling such environmental stresses and challenges. We shall not consider chronic pancreatitis to result from a one-time "hit", but rather, occurring as a result of repeated and multiple insults to an organ that is made susceptible by different influences.

Fig. 1. Picture of patient with tropical pancreatitis showing marked emaciation

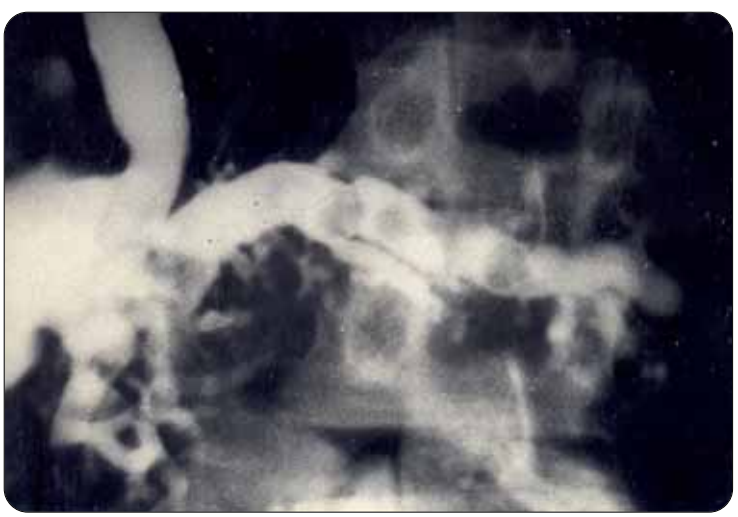

Fig. 2. ERCP picture of tropical pancreatitis showing calculi, ductal dilatation, strictures and irregularity

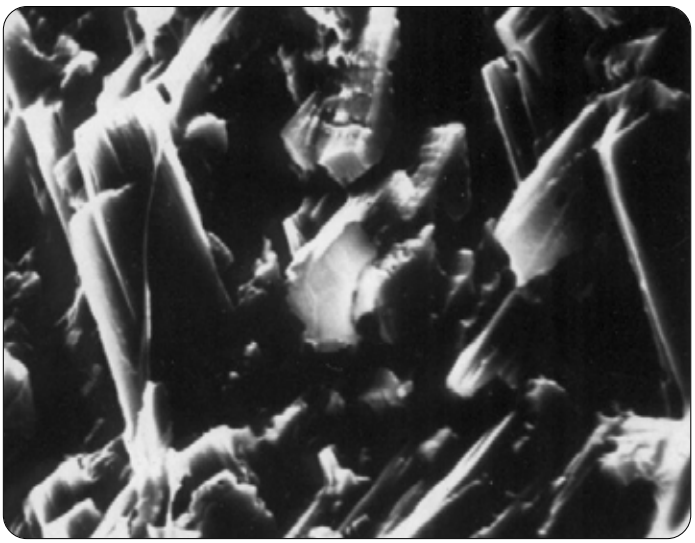

Fig. 3. Electron microscopy of pancreatic calculi from tropical pancreatitis showing heaps of calcium carbonate crystals

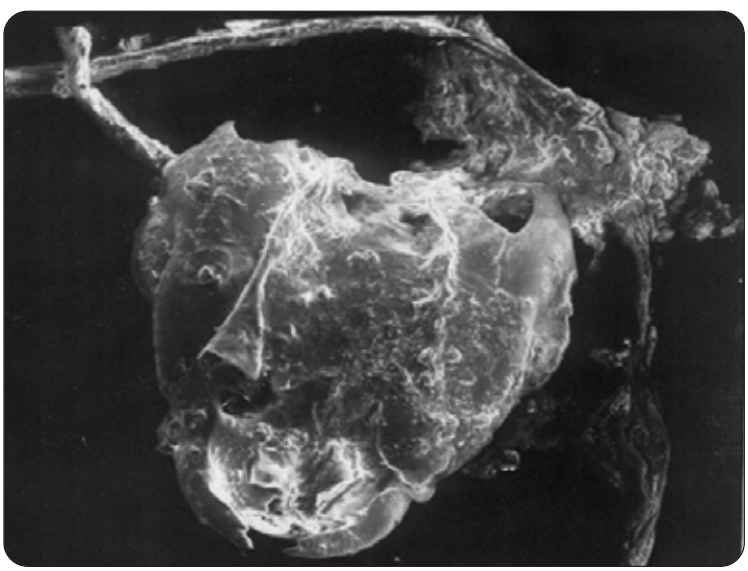

Fig. 4. Protein plugs from pancreatic duct showing fibres and amorphous deposits

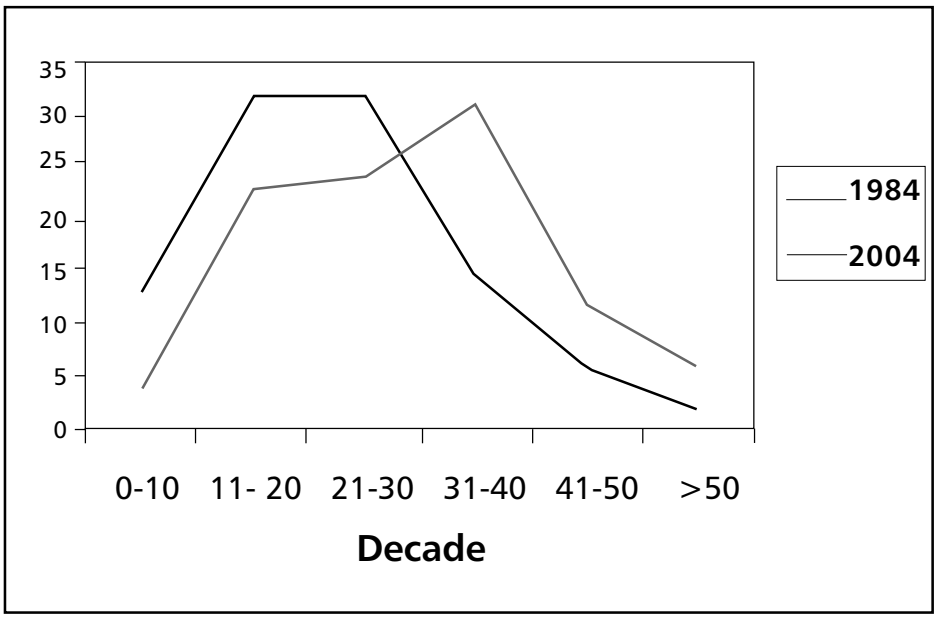

Fig. 5. Graph showing shift in the age of presentation of chronic pancreatitis patients

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References

1. Zuidema PJ. Calcification and cirrhosis of the pancreas in patients with deficient nutrition. Doc. Med. Geograph. Trop. Amsterdam 1955; 5: 229

2. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition: Trop Geog Med 1959; 11: 70-74.

3. Shaper AG. Chronic pancreatic disease and protein malnutrition: Lancet 1960; ii: 1223-1224.

4. Geevarghese PJ, Pillai VK, Pitchumoni CS. The diagnosis of pancreatogenous diabetes mellitus. J Assoc Phys Ind 1962; 10: 173-80.

5. Balakrishnan V. Pancreatic Tropicale In: Maladies Du Pancreas Exocrine (Eds.), Bernades, Hugier M. Doin, Paris 1987.

6. Kinnear TWG. The pattern of diabetes mellitus in a Nigerian teaching hospital: East African Medical Journal 1963; 40: 288-94.

7. Rajasuriya K, Thenabadu PN, Munasinghe DR. Pancreatic calcification in Ceylon with special reference to its etiology. Ceylon Medical Journal 1970; 15: 11-24.

8. Chandraprasert S, Samranvej P, Arthachinta S, Isarasena S. Diabetes mellitus and tropical form of chronic calcific pancreatitis in Thailand. Australian and New Zealand Journal of Medicine 1976; 6: 316-20.

9. Dani R, Penna FJ, Nogueria CED. Etiology of chronic pancreatitis in Brazil: a report of 329 consecutive cases. Int J Med 1976; 6: 316-320.

10. Balakrishnan, V, Meenu Hariharan, Sindhu S. Pathogenesis of Pancreatitis in India leading on to diabetes mellitus. Proc Nutr Soc India 1990; 36: 1-7.

11. Balakrishnan V, Sauniere JH, Hariharan M, Sarles H. Diet, pancreatic function and chronic pancreatitis in South India and France. Pancreas 1988; 3: 30-35.

12. Balakrishnan V, Hareendran A, Sukumaran Nair C. Double-blind cross-over trial of an enzyme preparation in pancreatic steatorrhoea. J Assoc Physician India 1981; 29: 207-209.

13. John Punnose, V Balakrishnan, A Bhadran et al. Exocrine Pancreatic Function in Chronic Pancreatitis with and without calcification. Indian J Gastroenterol; 1987; 6: 2: 85-86.

14. Naik S, Balakrishnan V, Hariharan M. HLA studies in chronic calcific pancreatitis. In: Proceedings World Congress on Tissue Antigens, Tokyo 1986.

15. Shenoy KT, Shanmugam J, Balakrishnan V. Viral and micoplasma pneumoniae antibodies in chronic pancreatitis of tropics. Indian J Med Res 1986; 84: 22-26.

16. Shanmugam J, Balakrishnan V, Molly George, Shenoy KT. Study of Coxsackie B viral infections in chronic pancreatitis patients from Kerala. Journal of Postgraduate Medicine 19897; 33: 29-31.

17. Raji EK, Balakrishnan V, Prabha B, Vasudevan DM. Immunological aspects of chronic calcific pancreatitis of Kerala (tropical pancreatitis). Abstracts of the 7th World Congress of Gastroenterology, Sweden 1982; 1801.

18. Balakrishnan V, Hariharan M, Rao VRK, Anand BS. Endoscopic pancreatography in chronic pancreatitis of the tropics. Digestion 1985; 32: 129-31.

19. Balakrishnan V. Tropical pancreatitis – Epidemiology, pathogenesis and etiology In: Chronic Pancreatitis in India (Ed.), Balakrishnan V. Indian Society of Pancreatology 1987.

20. Harada H, Neda U, Yasuoka M. Scanning electron microscopic studies on protein plugs obtained from patients with chronic pancreatitis. Gastroenterol Jpn 1982; 17: 98.

21. Rani M, Shah S. Worlds apart: why are Kerala and Uttarpradesh so different in human development outcomes? World Development Report 2004; Washington DC; World Bank 2004.

22. Ramasundaram P, Lakshim KR, Ananthanarinan M. Changing scenario of Cassava in Kerala Economy. International Symposium on Tropical Tuber Crops – Problems, Prospects and Future Strategies. Abstracts of Papers. Central Tuber Crops Research Institute, Trivandrum, India; Nov. 6-9, 1993: 69.

23. The Hoax of God's Own Country. Outlook Magazine; July 12, 2004: 53.

24. Durbec J, Sarles H. Multicenter survey of the etiology of pancreatic diseases. Relationship between the relative risk of developing chronic pancreatitis and alcohol, protein and lipid consumption. Digestion 1978; 18: 337-350.

25. Yingong Lin, Akiko Tamakoshi, Tetsuo Hayakawa et al. Cigarette Smoking as a Risk Factor for Chronic Pancreatitis: A Case-Control Study in Japan. Pancreas; 2000; 21: 109-114.

26. Lowenfels AB. The Epidemiology of Pancreatic Cancer. The Lustgarten Foundation for Pancreatic Cancer Research Annual Conference, Utah, Sep. 2004.

27. Balakrishnan V. Changing trends in the Natural History of Tropical Pancreatitis. Journal of Gastroenterology and Hepatology; 19: suppl. 2004 (Abstracts).

28. Sandeep S. Sidhu, Samiran Nandy, Tandon RK. The Effects of The Modified Puestow Procedure on Diabetes in Patients with Tropical Chronic Pancreatitis – A Prospective Study. The American Journal of Gastroenterology; 2001; 96: 1.

29. Eesh Bhatia, Gourdas Choudhuri, Sadiq S. Sikora et al. Tropical Calcific Pancreatitis: Strong Association with SPINK1 Trypsin Inhibitor Mutations. Gastroenterology 2002; 123: 1020-1025.

30. Shaper AG. Aetiology of chronic pancreatic fibrosis with calcification seen in ligandh. BMJ. 1964; 1: 1607.

31. Geevarghese PJ. In. Chronic Pancreatitis and Diabetes Mellitus in the Tropics. Varghese Publishing House, Bombay; 1992. 57-60.

32. Geevarghese PJ. In. Calcific Pancreatitis. Varghese Publishing House, Bombay. 1986: 62.

33. Tuescher T, Rosman JB, Baillod R et al. Absence of diabetes in rural West African population with a high carbohydrate/cassava diet. Lancet 1987; i: 765-768.

34. Braganza JM. Free radicals and pancreatitis. In: Rice-Evans C, Dormandy TC (Ed.), Free radicals: chemistry, pathology and medicine, Richelien Press, London 1988; 357-381.

35. Braganza JM, Mohan V. Xenobiotics in tropical chronic pancreatitis. In: Braganza JM (Ed.). Pathogenesis of Pancreatitis, Manchester University Press, New York, 1991; 115-128.

36. Balaraman Nair M, Latha P. Pancreas in chronic calcific pancreatitis. In: Chronic pancreatitis in India (Ed.) Balakrishnan V. Indian Society of Pancreatology 1987; 113-121.

37. Sandhyamani S. Mucoid vasculopathy: Vascular lesions in an autopsy study. Mod Pathol 1993; 6: 333-341.

38. Sandhyamani S, Vijayakumari A, Balaraman Nair M. Bonnet monkey model for pancreatic changes in induced malnutrition. Pancreas 1999; 18: 84-95.

39. Sarles H, Sauniere JF, Balakrishnan V, Attia Y, Dani R. Enquete nutritionnelle pluricentrique sur les facteurs etiologiques possibles de la pancrlatitite chronique tropicale. Bull Acad. Natle. Med. 1987; 171: 233-238.

40. Cristina Rigamoiti, Elisa Mottaran, Emanuela Reale et al. Moderate Alcohol Consumption Increases Oxidative Stress in Patients With Chronic Hepatitis C. Hepatology 2003; 38: 42-49.

41. Whitcomb DC, Gorry MC, Preston RA, Furey W, Jossenheimer MJ, Ulrich CD, Martin SP, Gates JR. LK, Amann ST, Toskes PP, Liddle R, McGrath K, Vomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nature genetics 1996; 14: 141-145.

42. Sharer N, Schwarz M, Geraldine M, Howarth A, Painter J, Super M, Braganza J – Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. NEJM 1998; 339: 645-652.

43. Pfutzer RH, Barmada MM, Brunskill AP, Furich R, Hart PS, Neoptolomos J, Furey WF, Whitcomb DC. SPINK 1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology 2000; 199: 615-623.

44. Chandak GR, Idris MM, Reddy DN, Bhaskar S, Sriram PVJ, Singh L. mutations in the pancreatic secretory trypsin inhibitor gene (PSTI/SPINK1) rather than the cationic trypsinogen gene (PRSS1) are significantly associated with tropical calcific pancreatitis. J Med Genet 2002; 30: 347-351.

45. Balakrishnan V. Chronic Calcific Pancreatitis in the Tropics. Editorial. Indian J Gastroenterol 1984; 3: 2: 65-67.

Chapter 3

Tropical pancreatitis in North India

Gourdas Choudhuri, Eesh Bhatia, Sadiq S Sikora, George Alexander

Summary

While tropical calcific pancreatitis (TCP) was first reported in Kerala, the disease is prevalent throughout India. At our center in North India, we found a high frequency of SPINK1 N34S mutations. In addition, 80% of our patients belonged to the middle or upper income groups. Similarly, only half of our patients were lean, less than a third had low serum albumin levels, while parotid gland enlargement and nutritional edema were not encountered. Patients with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. In older reports, as well as in some recent studies, most FCPD patients had severe insulin-requiring diabetes at onset. In our studies, we found that surgery does indeed improve pain and exocrine function, but recovery of endocrine dysfunction is a controversial issue.

Introduction

Tropical calcific pancreatitis (TCP) is a unique form of chronic, non-alcoholic pancreatitis, which is limited to the tropical developing countries. Patients present at a young age with severe abdominal pain, weight loss and insulin-requiring diabetes. The pancreas is often shrunken with dilatation of the main pancreatic duct due to multiple intraductal calculi and strictures. At time of presentation patients have markedly diminished pancreatic exocrine function and beta cell reserve. A subset of patients with TCP presents with diabetes without significant abdominal pain. This subset is also known as fibrocalculous pancreatic diabetes (FCPD).

The disease has most commonly been reported from Kerala, but is prevalent throughout India. The etiology of TCP is obscure. Established risk factors such as alcohol intake, hyperparathyroidism and biliary stones are absent. It has been proposed that environmental factors, such as protein energy malnutrition or the consumption of cassava (a source of cyanogenic glycosides) may play a pathogenic role. However, TCP is frequently found in regions where cassava is not consumed and is also observed in patients from higher economic levels, in whom malnutrition is unlikely. The familial clustering of TCP suggests that genetic defects may predispose to the disease.

TCP in North India

One of the genetic causes of TCP that has been identified is mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. Several reports from the world have shown that such mutations in the CFTR gene are high in patients with idiopathic pancreatitis. Many subjects with CFTR mutations diagnosed in childhood, present in adulthood with chronic pancreatitis. We tried to detect mutations in the entire CFTR gene by the multiplex heteroduplex analysis and direct sequencing in 18 consecutive TCP patients. (*Bhatia E et al. AJG 2000*). The screening comprised of the promoter region as well as all 27 exons including flanking intron sequences with estimated mutation detection rate of 95%. The patients were also tested for the 5-thymidine variant of the polythymidine tract of intron 8. CFTR gene mutations , including the 5T variant, were detected in only 2 (11%) TCP subjects, both females. The overall frequency of CFTR gene mutations was 0.083 (3/36), which is far lower than that observed in white Caucasian subjects with idiopathic chronic pancreatitis (0.20-0.24). Among female patients, the gene frequency was 0.25 (3/12), similar to that reported by Cohn et al (0.20, 9/44). This higher apparent frequency of CFTR mutations among female patients with TCP is of interest, because a female preponderance among patients with idiopathic pancreatitis is also a consistent observation. Based on the very low frequency of CFTR gene mutations in our patients, we concluded that this genetic abnormality had a very small etiologic role, if at all, in our patients with TCP.

Chronic pancreatitis is thought to result from inappropriate trypsin activity within the pancreatic parenchyma. Protective mechanisms capable of inactivating any trypsin activated within the pancreas prevent autodigestion in normal subjects, but these fail to act upon mutated trypsin. Gain-of-function mutations of the cationic trypsinogen (PRSS1) gene have been found to be associated with hereditary chronic pancreatitis. However its role in TCP appears unlikely. Pancreatic secretory trypsin inhibitor (serine protease inhibitor, Kazal type 1; SPINK 1) is a 56-amino-acid peptide that specifically inhibits trypsin by physically blocking its active site and acts as the first line of defence against prematurely activated trypsinogen. Mutations in the SPINK1 gene have been reported to be associated with chronic pancreatitis in Europe and the United States and a substitution of asparagines by serine (N34S) in

exon 3 was the most common SPINK1 mutation found in them. We prospectively studied these two mutations (PRSS1 and SPINK1) in 66 of our TCP patients. (*Bhatia E et al. Gastroenterology 2002*) Twenty-nine patients (44%) carried the N34S missense mutation, of which 9(14%) were homozygotes. In contrast only 2 (2.2%) control subjects were N34S heterozygotes ($p<0.001$), suggesting a strong association of this genetic mutation with TCP. We noted however that in patients with TCP the frequency of N34S carriers and homozygotes were similar in those with or without diabetes. The high frequency of SPINK1 N34S mutation in our patients with TCP compared with controls suggested a possible etiologic or predisposing role in a subset of our patients. Our observation that the frequency was similar in TCP patients with and without diabetes suggests that these two subtypes have a similar genetic predisposition. Mutations in the PRSS1 gene were not detected in any patient, confirming earlier reports and suggesting that mutations in this gene are not associated with TCP. While these findings are exciting, few new questions arise. In our study, N34S homozygotes did not reveal greater severity in their clinical features, when compared with heterozygotes. This would suggest that while a heterozygous N34S mutation is strongly associated with TCP, it might not be adequate to cause the disease without other genetic and/or environmental factors.

Earlier reports described the disease as occurring among adults of a poor socioeconomic status. The patients presented with emaciation, nutritional deficiencies and severe IDDM (but ketosis resistant). The prognosis was described as dismal with most patients succumbing to the disease within a few years of diagnosis. More recently Yajnik et al from Pune have described a high mortality rate from infections and acute complications related to diabetes among FCPD patients. But as a result of improvements in the socioeconomic status and standards of medical care, the clinical presentation and prognosis of patients with TCP have changed.

Of 270 patients of chronic pancreatitis being followed up in our pancreatic clinic, 150 (55.5 %) had TCP. The median age of onset of pancreatitis in these patients was 23.2 +/- 6.2 years. Fifty-eight percent of patients had onset of pain at age less than 20 years. On presentation 26 % had diabetes mellitus and a further 26 % developed diabetes on follow-up. In patients in whom diabetes appeared after pain, the median

time of onset of diabetes after symptoms of pancreatitis was 59.7 +/- 24.5 months. The patients' body mass index (BMI) was 18.1 +/- 3.4 kg/m2; a low BMI (<18 kg/m2) was found in 53% of the patients at presentation. Pain was a prominent symptom and it was seen that the duration of pain was longer in those who had diabetes compared to those without.

Calcification was seen in 57% patients of TCP of whom 47% had diabetes. In patients without calcification diabetes was present in only 17.5 % ($p<0.05$). Most of the patients had severely diminished exocrine function with mean fecal chymotrypsin being 2.2 +/- 2.2 U/g stool. Thirty-three percent of patients with exocrine deficiency (low fecal chymotrypsin) had diabetes compared to 40 % in those without exocrine deficiency. ($p=ns$) Therefore development of diabetes mellitus in patients with TCP was related to the duration of pain and calcification and not to presence or absence of exocrine deficiency. Comparing our patients with TCP without diabetes with those with FCPD, we did not find any significant difference in median age, age at onset of pain, BMI or degree of exocrine insufficiency (fecal chymotrypsin).

Eighty of our patients of FCPD were separately evaluated for their nutritional status, clinical presentation, beta-cell function and exocrine function (*Mittal N et al. Nat Med J of India 2002*). The patients in our study differed in many aspects from those reported earlier. In previous reports TCP occurred predominantly in economically deprived people, who were emaciated and suffered from numerous nutritional deficiencies. In contrast, 80% of our patients belonged to the middle or upper income groups. Similarly, only half of our patients had a low BMI, less than a third had low serum albumin levels, while parotid gland enlargement and nutritional edema were not encountered. Patients with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. In older reports, as well as in some recent studies, most FCPD patients had severe insulin-requiring diabetes at onset. In contrast in our study, 2/3 were initially controlled on diet or oral hypoglycemic agents. The only clinical characteristics differentiating patients requiring diet/oral medications or insulin were that the latter were younger and had worse glycemic control. Fasting C-peptide levels did not differ significantly between these two groups of patients.

In our study as well in previous studies, beta cell function varied widely at presentation. (*Mehrotra R et al. Metabolism 1997*) This may be the result of a variable rate of loss of beta cell function or because patients presented at different stages of pancreatitis. We also observed that beta cell function was negatively associated with a longer duration of diabetes. This is the likely reason for a large proportion of our FCPD patients on diet/oral medications requiring insulin within 5 years of diagnosis. We detected a high prevalence of microvascular complications in this population and the prevalence increased with duration. But unlike type 2 diabetes none of the patients with duration of diabetes less than 2 years had any microvascular complications. This may reflect the relatively abrupt onset of symptoms of hyperglycemia in most FCPD patients.

In contrast to beta cell function, exocrine function was markedly diminished in all FCPD patients by time of presentation. There was no correlation between FCT and C-peptide levels. It is possible that by the time glucose intolerance manifests, exocrine function is already markedly diminished in most patients. Our data are in contrast to an earlier study by Yajnik et al, in which beta cell and exocrine function were directly correlated. Despite having severely diminished FCT levels, most of the patients exhibited a sustained and significant improvement in weight on enzyme supplements. In our prospective study of 32 patients of FCPD, only 2 (6 %) died. Renal failure and carcinoma of pancreas were the cause of mortality. These data are in contrast to older studies, and to a more recent study by Yajnik and Shelgikar, where a high mortality rate was observed mainly due to infectious diseases, malnutrition and acute diabetes-related complication.

The exact pathogenesis of pain and progressive pancreatic dysfunction in chronic pancreatitis is not clear. Increased intraductal pressure and its effects on the pancreatic parenchyma, may play a role in a subset of patients who present with dilatation or strictures. In these patients with "obstructive pancreatitis", the pain responds well to decompressive procedures. We conducted a prospective study to evaluate the effect of drainage of the pancreatic duct on beta cell and exocrine function in TCP patients. (*Agarwal G et al. World J Surg 2002*) While the pain score improved significantly following ductal decompression, there was no

change in beta cell function. FCT was diminished in all patients prior to intervention and did not normalize after ductal drainage in any patient. All 4 subjects with elevated baseline trypsin levels had a sharp fall after intervention. However serum trypsin did not normalize after ductal drainage in any patient with a diminished baseline value. A fall in elevated trypsin suggests that there may be relief of subclinical inflammation after intervention, however there is no improvement in exocrine function after a follow up of 1 year.

References

1. Bhatia E, Durie P, Zielenski J, Lam D, Sikora SS, Choudhuri G, Tsui LC. Mutations in the cystic fibrosis transmembrane regulator gene in patients with tropical calcific pancreatitis. Am J Gastroenterol 2000; 95:3658-3659
2. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, Witt H. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. Gastroenterol 2002; 123:1020-1025
3. Mittal N, Mehrotra R, Agarwal G, Rajeshwari J, Choudhuri G, Sikora S, Bhatia E. The clinical spectrum of fibrocalculous pancreatic diabetes in north India. The Nat Med J of India 2000; 15:327-330
4. Mehrotra R, Bhatia E, Choudhuri G. Beta-cell function and insulin sensitivity in tropical calcific pancreatitis from north India. Metabolism 1997; 46:441-444
5. Agarwal G, Sikora S, Choudhuri G, Bhatia E. Prospective study of pancreatic beta cell and exocrine function following duct decompression in tropical calcific pancreatitis. World J Surg 2002; 26:171-175

Chapter 4

Chronic pancreatitis: the AIIMS, New Delhi experience

Pramod K Garg

Summary

Tropical pancreatitis is a special type of chronic pancreatitis that is seen mainly in tropical countries. The prevalence of tropical pancreatitis is not known in northern India. The etiology is not known; genetic mutation such as SPINK1 gene mutation and environmental factors are the likely culprits. We have found SPINK 1 mutation in about 40% of our patients with idiopathic chronic pancreatitis. The disease usually affects young patients. Clinically, >90% of patients present with abdominal pain. About 25% of patients develop diabetes that generally requires insulin for its control but is ketosis resistant. Painless diabetes is another clinical presentation in some patients. Most patients develop malnutrition during the course of the disease. We have found that malnutrition is not a cause but an effect of the disease. Steatorhoea is less common. The diagnosis can be established by plain x-ray of the abdomen, ultrasonography, a computerized tomography scan of the abdomen or ERCP. Management is directed towards pain relief and control of diabetes and steatorhoea. Pain relief can be obtained by analgesics and enzyme supplementation with high protease content. Endotherapy coupled with stone fragmentation by ESWL is an effective therapy in about 50% of our patients. Surgical decompression of the main pancreatic duct by lateral pancreato-jejunostomy is reserved for patients with severe pain non-responsive to other forms of therapy.

Introduction

Tropical pancreatitis (TP) is a type of chronic pancreatitis seen in tropical countries and is characterized by pancreatic calcification and ductal dilatation in a young malnourished patient who presents with abdominal pain and/or diabetes[1]. Initially described from Indonesia, [2] it has been reported from many other tropical countries including India, Nigeria, Uganda, West Indies, Kenya, Sri Lanka, Madagascar and Zaire[3,4] and recently from others parts of India (6) and other countries such as China (7). It has been called by a variety of names such as chronic calcific pancreatitis of the tropics, juvenile tropical pancreatitis syndrome, idiopathic chronic calcific pancreatitis of the tropics, nonalcoholic tropical pancreatitis and nutritional pancreatitis. The largest series has however, been described from South India by Geevarghese[7].

Epidemiology and clinical features

The prevalence of tropical pancreatitis is estimated to be ~126/100,000 population) in southern India according to a survey conducted by Balaji et al from the department of Gastroenterology, AIIMS, New Delhi (8). This is in contrast to the estimated prevalence of chronic pancreatitis of around 10-15/100,000 population in several western industrialized countries and 45.4/100,000 population in Japan [9,10]. Such a high prevalence of chronic pancreatitis in India suggests that it is an endemic zone for CP and points towards a possible genetic and/or environmental factor as playing an important etiologic role.

Most patients with CP are young in our experience, the mean age being 36.7 years. The majority of patients were male i.e. 80%. The duration of disease from the time of presentation to the hospital was 48 months.

Pain was the most common mode of presentation, being present in 97% of patients. The prevalence of diabetes in patients with CP was 31% but the prevalence of clinical malabsorption (maldigestion) was much lower at 5% (Table 1).

Among the complications (Table 2) of CP, pseudocysts were present in 32% of patients, bile duct stricture in 3.5% of patients, and splenic vein thrombosis in 7% of patients. The prevalence of cancer was in 2.2% of patients with TP.

The clinical features of hospital based TP patients also differed from those of alcoholic pancreatitis in many respects (table 3).

How is TP different from other forms of chronic pancreatitis?

The following features in a patient are characteristic of TP and distinguish it from other types of CP: young age of onset, residence in tropics, no history of alcoholism, no other discernible cause of CP, negative family history of pancreatitis, large duct disease with ductal dilatation, large pancreatic calculi predominantly in the head region, presentation with chronic abdominal pain, diabetes which is insulin requiring but ketosis resistant and finally, the coexistence of malnutrition.

Etiology

Tropical pancreatitis forms about 59 % of all our patients with chronic pancreatitis[6]. The etiology of tropical pancreatitis is not known and is still considered idiopathic. However, certain potential etiological factors have been identified. Among them, genetic predisposition is most likely. These factors are discussed below.

Malnutrition

Protein calorie malnutrition has long been suspected as a likely cause for TP because of the fact that the disease occurs predominantly in tropical countries where malnutrition is common and because of the reports from some of them including India, Uganda and Nigeria reveal that 80-90% of the subjects with calcific pancreatic come from poor socio-economic strata. Chronic protein undernutrition leads to structural as well as functional alterations in the pancreas. It also makes females more susceptible to pancreato-toxins. However, severe malnutrition is not associated with chronic pancreatitis but with pancreatic atrophy and insufficiency[11,12].

In a prospective study of 105 north Indian patients with chronic pancreatitis, we found that the mean BMI of patients was 22.89±3.28 which was similar to that of controls. Only 12% of patients had a BMI <18.5. On the other hand, 80% of patients lost weight following the onset of disease and the percentage of patients with BMI <18.5 increased from12% to 52%. The causes of weight loss were found to be (i) significant decrease in calorie intake due to pain compared with the recommended intake (1437±574 vs. 2605±313 kcal), (ii) subclinical steatorrhea in 60%, and (iii) diabetes in 29%. These data suggested that malnutrition was a not a cause but an effect of tropical pancreatitis[13].

Environmental toxins

The toxic hypothesis has been centered on consumption of cassava which has cyanogenic glycoside and is used liberally in southern India where TP is endemic.[14] This theory has also not found wide acceptance because

of the following reasons: (i) cassava does not feature in the diet of many people who develop TP; (ii) there was no difference in cassava consumption between patients with TP and those without[15]; (iii) patients with TP from northern India do not consume cassava, and (iv) long-term cassava consumption did not produce diabetes or pancreatitis in a rat model[16].

Free radical Injury

Braganza et al have shown that patients with alcoholic pancreatitis as well as other forms of chronic pancreatitis including TP are deficient in antioxidants and hence are more vulnerable to free radical injury[17]. They have further shown that supplementation with antioxidants may result in a significant decrease in analgesic requirements in patients with alcoholic pancreatitis [18]. We have also found that patients with TP do have increased free radical mediated injury as evidenced by high levels of malondialdehyde and decreased anti-oxidant levels[19]. In a recent ongoing study on the oxidative stress (OS) and total antioxidant capacity (TAC) in 48 consecutive patients with TP, we measured oxidative stress by lipid peroxidation products (LPO) and superoxide dismutase (SOD), and antoioxidant capacity by Ferric reducing ability of plasma. Our results showed that patients with chronic pancreatitis had increased oxidative stress and decreased antioxidant capacity (Figure 1, 2)

Genetic factors

The landmark discovery by Whitcomb et al of a mutation in the gene for cationic trypsinogen on the long arm of chromosome 7 (7q35) in patients with hereditary pancreatitis verified the long held belief that a genetic defect underlies hereditary pancreatitis[20]. A lot of interest has recently been generated in the possibility that there may be a genetic basis for TP because of the following similarities between TP and hereditary pancreatitis: (i) both diseases affect young individuals; (ii) calcification is very common in both; and (iii) there is an increased risk of pancreatic cancer in both. Moreover, Indians born in Kerala, but residing outside India continue to have an increased prevalence of TP[15]. An association of HLA DQ 9(A*0201-B*03003) has been shown with TP and diabetes (FCPD or fibrocalculous pancreatic diabetes)[21]. However,

one study from Bangladesh failed to show any mutation of the cationic trypsionogen gene among 13 patients with TP[22]. Another study did not find cationic trypsinogen gene mutation in 46 patients with FCPD[23].

Two groups demonstrated that the expected frequency of CFTR gene mutation was much higher among patients with idiopathic chronic pancreatitis i.e. 2.5 and 11.5 times the expected frequency seen in the general population [24,25]. Affected patients with chronic pancreatitis were shown to have single gene CFTR mutations and/or 5T allele in intron 8 which resulted in a reduced activity of CFTR. In patients with typical cystic fibrosis, there are severe mutations affecting both alleles; the result is pancreatic insufficiency caused by atrophy of the pancreas. On the other hand, a mutation affecting only one allele may result in diseases such as chronic pancreatitis while retaining 'pancreatic sufficiency'.

More recently, a mutation in the pancreatic secretory trypsin inhibitor (PSTI, also known as serine protease Inhibitor Kajal type 1 or SPINK1) (N34S, chromosome 5) was found in 23% of patients with idiopathic pancreatitis versus 2% in the general population[26]. SPINK I inhibits trypsin within the pancreas but accounts for inactivation of only ~20% of all activated trypsin [27]. It is therefore unlikely that the SPINK I mutation alone will cause pancreatitis, but it might be a disease modifier lowering the threshold for pancreatitis [28]. SPINK 1 mutation has been found in 32-44% of patients with TP from India [29,30].

We have analysed patients with chronic pancreatitis for common CFTR and SPINK1 gene mutations. One hundred patients with TP were studied for SPINK1 N34S mutation and CFTR gene mutation forDelta F508 and Intron 19 (3849+10 Kb C>T) and common variant of poly (T) sequence in intron 8 of *CFTR gene* (5T, 7T, 9T). We found 40% of patients having SPINK 1 gene mutation (table 4).

At present, intense search is on in many laboratories around the world to discover more mutations in patients with CP. There is every possibility that, in the near future, the genetic basis of CP will be further clarified. Further genetic analyses are also urgently required in patients with TP.

Diagnosis

The diagnosis of TP is based on a combination of clinical evaluation and imaging studies. In advanced disease, a plain film of the abdomen or a contrast enhanced computerized tomography (CECT) may show the pancreatic calcification and establish the diagnosis. In early cases, demonstration of ductal changes through endoscopic retrograde cholangio-pancreatography (ERCP) or magnetic resonance cholangio-pancreatography (MRCP) will establish the diagnosis. Pancreatic function tests are indeed the most sensitive tests to detect earliest changes in the exocrine pancreas[31] but they may be abnormal in any cause of pancreatic insufficiency e.g. cystic fibrosis and not necessarily in chronic pancreatitis. Endoscopic ultrasonography has been touted as the most sensitive method of detecting earliest changes of pancreatitis in the parenchyma but its value remains to be established (Figure 3) [32]. The gold standard for diagnosis is histopathology but that is rarely obtained unless the patient undergoes a pancreatic resection.

Consequences of tropical pancreatitis

Tropical pancreatitis can lead to endocrine and exocrine insufficiency like any other chronic pancreatitis, the difference being that the degree of functional impairment is much more pronounced and early in tropical pancreatitis compared with other forms of chronic pancreatitis. Exocrine impairment leads to maldigestion and steatorrhea. Clinical steatorrhea is uncommon even in patients with advanced TP largely due to restriction of fat consumption by the patients. Steatorrhea can be managed well with supplementation of oral pancreatic enzymes with high lipase content.

Endocrine insufficiency leads to pancreatic diabetes. Diabetes is present in 25-90% of patients with tropical pancreatitis. Such a wide difference in the prevalence of diabetes is mainly due to the referral pattern. Patients presenting with diabetes as the major clinical problem get referred to diabetes clinics and data coming from such clinics often report a high prevalence of diabetes in patients with TP. On the other hand, diabetes is prevalent in about 31% of patients with TP in our gastroenterology clinic. There are many special characteristics of diabetes in TP which are discussed below.

Diabetes in TP

Patients with TP develop diabetes during the course of the disease. Patients with calcification are more likely to develop diabetes. Overall, up to 60% of patients with TP may develop diabetes. Many patients with painless TP present primarily with diabetes. These patients are initially misdiagnosed as having insulin requiring diabetes mellitus (IDDM). Fibrocalculous pancreatic diabetes (FCPD) is the term given to patients with painless calcific pancreatitis with diabetes[33]. FCPD was earlier classified as malnutrition related diabetes mellitus (MRDM) by the WHO because most of the patients with FCPD are malnourished. Diabetes in patients with tropical pancreatitis is described as particularly severe, requiring high doses of insulin. Diabetes may be brittle in patients with TP with frequent episodes of hypoglycemia. This may be due to concomitant exocrine insufficiency. Patients with pancreatic diabetes usually require insulin for its control but the characteristics feature is that they are ketosis resistant even if insulin is withheld. The possible reasons for ketosis resistance are better insulin reserve compared with IDDM and low glucagon response to glucose load[33, 34]. It was believed that more than 90% of patients with TP would require insulin for the control of diabetes. However, the current experience has shown that up to one third of patients of patients can be managed with oral hypoglycemic agents[6]. The insulin requirement was also thought to be very high up to 100 units per day but it has been shown that the majority of patients can be managed with regular doses of insulin. Patients with diabetes and TP may develop all macro- and micro-vascular complications of poorly controlled diabetes if they survive long enough[33].

Management

Medical treatment of TP is similar to that of any chronic pancreatitis and is aimed at relieving pain and steatorrhoea and controlling diabetes[1].

Pain relief

For pain relief, initially non-opioid and later, opioid analgesics are used. Another approach has been to use pancreatic enzymes (proteases) based on the understanding that delivering these enzymes in the duodenum

could result in suppression of cholecystokinin (CCK) and hence a decrease in pancreatic exocrine secretion. Their role in relieving pain is however, questionable. The results of a meta-analysis of 6 randomised controlled trials showed no benefit of enzyme therapy in relieving pain [35]. However, non-enteric coated pancreatic enzyme supplementation may relieve pain in patients with small pancreatic duct disease, idiopathic pancreatitis and in female patients[36]. The Asia-Pacific consensus report on chronic pancreatitis also suggests pancreatic enzymes and non-opioid analgesics as the initial therapy for pain relief in patients with chronic pancreatitis[1].

Use of antioxidants has also been suggested recently for pain relief in chronic pancreatitis. A combination of antioxidants containing at least 2 grams of methionine per day may help relieve pain if continued for about a year[37]. We have also shown that anti-oxidant supplementation relieves pain in tropical pancreatitis[38].

Surgery is required predominantly for intractable pain in about a third of patients. Its results are good only in patients with dilated ductal system which is the case in the majority of TP patients. The most common operation performed is lateral pancreatojejunostomy (modified Puestow's operation). In a study from our department, relief of pain was obtained in 90% of patients at 3 months after the operation and this relief was long lasting (5 years) in 82% of patients[39]. The results of surgical drainage are less gratifying in chronic pancreatitis in the western world[40], as the predominant etiology there is alcohol abuse and the behaviour of alcoholic chronic pancreatitis may be different from that of TP.

Endoscopic therapy

What has been achieved by surgery can now be done by endoscopy. Thus, dilated pancreatic ductal system can be decompressed by endoscopic sphincterotomy and pancreatic ductal stone clearance by a combination of basketing and extracorporeal shock wave lithotripsy (ESWL). And these maneuvers have indeed yielded gratifying results. Various endoscopic series have reported 50-70% success for clearing the main pancreatic duct and 60-80% long term pain relief with

complications of <10% [41-43]. We have also found good results of endotherapy in ~60% of patients with tropical pancreatitis[44]. The results of endoscopic treatment are comparable with the surgical results but the problem is that all endoscopic series have been case series and no controlled prospective trial is available. Furthermore, long term results need to be interpreted in the light of the fact that many patients get spontaneous relief from pain due to "burning out of the disease" [45]. Thus, it is important to find out the true benefit of endoscopic therapy in the long run. Randomized controlled studies comparing endoscopic and surgical treatment modalities are required. Till such time that these studies become available, however, most endoscopists would prefer giving a trial of endoscopic therapy before subjecting the patient to surgery if the medical therapy has failed as the initial results of endoscopic therapy are encouraging and the patients prefer less invasive procedures. One study has recently been published which has shown comparable results of surgical and endoscopic treatment for pain relief in chronic pancreatitis[46].

Conclusion

TP is a type of idiopathic CP that occurs in the tropics, but is also seen in northern India. It affects young patients. Its diagnosis is established by clinical evaluation and imaging, particularly plain film of the abdomen, ultrasound and/or CT scan of the abdomen showing pancreatic calculi. Many etiological factors have been suspected but genetic mutations, especially in the SPINK 1 gene appear as the most likely cause. Treatment is aimed at relieving pain and steatorrhoea and controlling diabetes.

Fig. 1: Oxidative stress in patients and controls

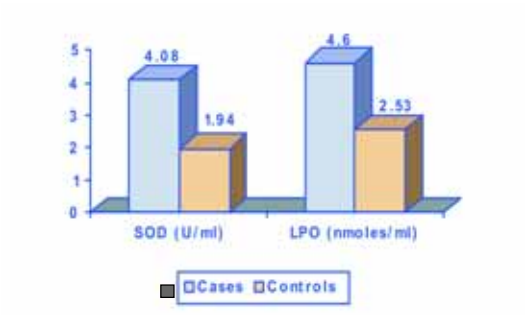


Fig 2: Antioxidant status of patients and contorls

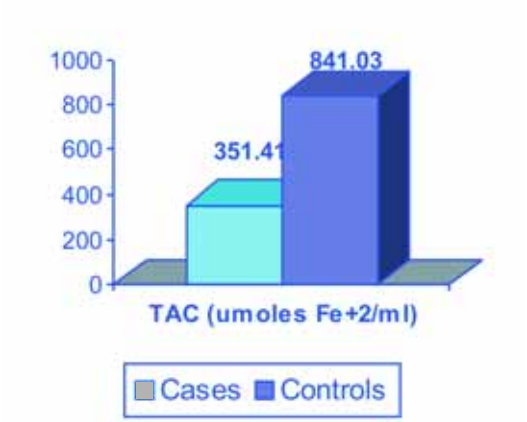
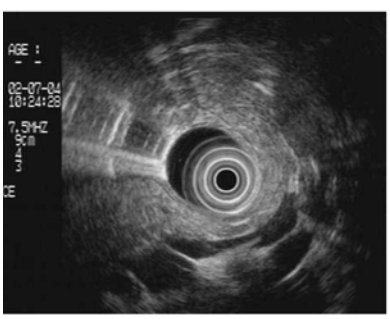


Fig. 3: EUS picture of (A) normal pancreas and (B) early chronic pancreatitis with honeycombing appearance



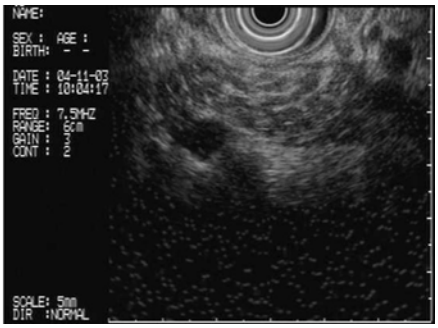


Table 1: Clinical features of patients with chronic pancreatitis

No. of patients	359
Mean age (years)	36.7
Sex (male : female)	4:1
Duration of disease (months)	48
Pain (%)	97
Diabetes (%)	31
Steatorrhea(%)	5

Table 2: Complications of chronic pancreatitis

Pseudocyst (%)	32.0
Bile duct stricture (%)	3.5
Splenic vein thrombosis (%)	7.0
Cancer (%)	2.2

Table 3: Comparison of Idiopathic with Alcoholic pancreatitis

	Idiopathic(%)	Alcoholic(%)	'p'
Acute pain	24	61	<0.05
Chronic pain	73	36	
Calcification	88	50	<0.05
Diabetes	23	11	
Pseudocyst	25	36	
Steatorrhea	2	1	

Table 4: Gene mutations in chronic pancreatitis

Gene tested	Mutation	Homozygous	Heterozygous
CFTR (n=100)	DeltaF508 3849+10kb C>T	0	3
SPINK 1 (n=100)	N34S	6	34

References

1. Tandon RK, Sato N, Garg PK. Chronic pancreatitis: Asia-Pacific consensus report. J Gastroenterol Hepatol 2002;17: 508-18.

2. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Georg Med. 1959;11:70-74.

3. Sarles H, Payan H and Sahel J. Chronic pancreatitis, relapsing pancreatitis and calcifications of pancreas. In: Gastroenterology. 1976;3:1040-1051.

4. Diabetes mellitus. Report of a WHO study group Technical Report Series 727. World Health Organization, Geneva 1985.

5. Balakrishnan V. Chronic calcific pancreatitis in the tropics. Ind J Gastroenterol 1984;3:65-7.

6. Garg P and Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastroenterol Hepatol 2004; 19: 998-1004.

7. Geeverghese PH. Pancreatic diabetes; A clinicopathological study of growth onset diabetes with pancreatic calculi, Bombay: Popular Prakastan, 1968.

8. Balaji LN, Tandon RK, Tandon BN, Banks A. Prevalence and clinical features of chronic pancreatitis in southern India. Int J Pancreatol. 1994;15:29-34.

9. The Copenhagen pancreatic study group: An interim report from a prospective epidemiological multicentre study. Scand J Gastroenterol 1981;16:305-312.

10. Lin Y, Tamakoshi A, Matsuno S, Takeda K, Hayakawa T, Kitagawa M, Naruse S, Kawamura T, Wakai K, Aoki R, Kojima M, Ohno Y, Nationwide epidemiological survey of chronic pancreatitis in Japan . J Gastroenterol 2000;35:136-141.

11. Brooks SE, Golden MH. The exocrine pancreas in kwashiorkor and marasmus. Light and electron microscopy. West Indian Med J. 1992;41:56-60.

12. Balakrishnan V, Sauniere JF, Hariharan M, Sarles H. Diet, pancreatic function, and chronic pancreatitis in south India and France. Pancreas 1988;3:30-5.

13. Singh N, Sethi M, Garg PK, Joshi YK, Tandon RK. Malnutrition and chronic pancreatitis: A prospective study of cause and effect relationship. Indian J Gastroenterol 2002;21(suppl):A42.

14. Narendranathan M. Chronic calcific pancreatitis of the tropics. Tropical Gastroenterology 1981;2:40-5.

15. Narendranathn M, Cheriyan A. Lack of association between cassava consumption and tropical pancreatitis syndrome. J Gastroenterol Hepatol 1994; 9:282-5.

16. Mathangi DC, Deepa R, Mohan V, Govindaranjan M, Namasivayam A. Long-term ingestion of cassava (tapioca) does not produce diabetes or pancreatitis in the rat model. Int J Pancreatol. 2000;27:203-8.

17. Braganza JM, Schofield D, Snehalatha C, Mohan V. Micronutrient antioxidant status in tropical compared with temperate-zone chronic pancreatitis. Scand J Gastroenterol. 1993;28:1098-104.

18. Chouduary A, Garg PK, Tandon RK. The role of oxidative stress in tropical pancreatitis and effect of antioxidants supplementation on pain in patients with tropical pancreatitis. J Gastroenterol. Hepatol. 2001;16 (Suppl): A132(Abstract).

19. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Urich CD, Martin SP, Gates Jr LK, Amann ST, Toskes PP, Liddle R, McGrath K , Umomo G, Post JC, Ehrich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsionogen gene, Nat Genet 1996;14:141-145.

20. Sanjeevi CB, Kanungo A, Shtanvera A, Samal KC, Tripathi BB. Association with HLA class II alleles with different subgroups of diabetes mellitus in Eastern India identify different associations with IDDM and malnutrition related diabetes. Tissue Antigen 1999;54:83-7.

21. Rossi L, Whitcomb DC, Ehrich GD et al. Lack of R117H mutation in the cationic trypsinogen gene in patients with tropical pancreatitis from Bangladesh. Pancreas 1998;54:83-7.

22. Hassan Z, Mohan V, McDermott MF et al. Pancreatitis in fibrocalculous pancreatic diabetes mellitus is not associated with common mutations in the trypsinogen gene. Diabetes Metab. Res. Rev. 2000;16:454-7.

23. Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 1998;339:645-652.

24. Cohn JA, Friendman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998;339:653-658.

25. Makharia GM, Kabra M, Garg PK, Shastri SS, Tandon RK. Cystic fibrosis transmembrane conductance regulator gene mutations (rF508 AND 3849+10KB CàT) in patients with chronic calcific pancreatitis of tropics. J Gastroenterol Hepatol 2001 (suppl);16:A112.

26. Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, Landt O, Becker M. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000;25:213-216.

27. Rinderknecht H. Pancreatic secretory enzymes. In: Go VLW, DiMagno EP, Gardner JD, Lebenthal E, Reber HA, Scheele GA, eds. The Pancreas: biology, pathobiology and disease. 2nd ed. New York:Raven, 1993:219-51.

28. Pfutzer RH, Barmada MM, Brunskil APJ, Finch R, Hart PS, Neoptolemos J et al. SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology 2000;119:615-23.

29. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, Witt H. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. Gastroenterology. 2002;123:1020-5.

30. Chandak GR, Idris MM, Reddy DN, Mani KR, Bhaskar S, Rao GV, Singh L. Absence of PRSS1 mutations and association of SPINK1 trypsin inhibitor mutations in hereditary and non-hereditary chronic pancreatitis. Gut. 2004;53:723-8.

31. Homma T, Harada H, Koizumi M. Diagnostic criteria for chronic pancreatitis by the Japan Pancreas Society. Pancreas 1997;15:14-15.

32. Catalano MF, Lahoti S, Geenen JE, Hogan WJ. Prospective evaluation of endoscopic ultrasonography, endoscopic retrograde pancreatography, and secretin test in the diagnosis of chronic pancreatitis. Gastrointest Endosc. 1998;48:11-7.

33. Mohan V, Nagalotimath SJ, Yajnik CS, Tripathy BB. Fibrocalculous pancreatic diabetes. Diabetes Metab Rev 1998;14:153-70.

34. Sidhu SS, Shah P, Prasanna BM, Srikanta SS, Tandon RK. Chronic calcific pancreatitis of the tropics (CCPT): spectrum and correlates of exocrine and endocrine pancreatic dysfunction. Diabetes Res Clin Pract 1995;27:127-32.

35. Brown A, Hughes M, Tenner S, Banks PA. Does pancreatic enzyme supplementation reduce pain in patients with chronic pancreatitis: a meta-analysis. Am J Gastroenterol 1997;92:2032-5.

36. Warshaw AL, Banks PA, Fernandez Del Castillo C: American Gastroenterological Association technical review: Treatment of pain in chronic pancreatitis. Gastroenterology 1998;115;765-776.

37. McCloy R. Chronic pancreatitis at Manchester, UK. Focus on antioxidant therapy. Digestion 1998;59 Suppl 4:36-48.

38. Nandi B, Garg PK, Bhardwaj P, Prakash S, Tandon RK. Efficacy of antioxidants for pain relief in patients with chronic pancreatitis: A randomized controlled trial. Ind J Gastroenterol 2002;21(suppl):A43.

39. Sidhu SS, Nundy S, Tandon RK. The effect of the modified Puestow procedure on diabetes in patients with tropical chronic pancreatitis- A prospective study. Am J Gastroenterology 2001;96:107-111.

40. Izbicki RJ, Bloechle C, Knoefel WT, Rogiers X, Kuechler T. Surgical treatment of chronic pancreatitis and quality of life after operation. Surg Clin North Am 1999;79:913-44.

41. Delhaye M, Vandermeeren A, Baize M, et al. Extracorporeal shock-wave lithotripsy of pancreatic calculi. Gastroenterology 1992;102:610-20.

42. Adamek HE, Jakobs R, Buttmann A, Adamek MU, Schneider AR, Riemann JF. Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy. Gut 1999;45:402-5.

43. Rosch T, Daniel S, Scholz M, et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy 2002;34:765-71.

44. Garg PK, Seth A, Gupta NP, Tandon RK. Endoscopic pancreatic sphincterotomy plus extracorporeal shock wave lithotripsy is effective treatment for tropical pancreatitis. J. Gastroenterol. Hepatol. 2000;15(Suppl): A204(Abstract).

45. Ammann RW, Akovbinatz A, Largiader F et al. Course and outcome of chronic pancreatitis. Gastroenterology 1984;86:820-8.

46. Dite P, Ruzicka M, Zboril V, Novotny I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy 2003;35:553-8.

Chapter 5

Profile of chronic pancreatitis at the PGIMER, Chandigarh

Deepak Bhasin, Gursewak Singh, Nagi B, Shoket M Chowdry

Summary

In this article, we discuss the profile of chronic pancreatitis as seen at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. Patients presenting with pain and idiopathic pancreatitis formed the commonest group studied. Pancreatic pseudocysts were the commonest complication. In this article, we also present our experience with endotherapy as well as lithotripsy in this setting.

Introduction

Chronic pancreatitis refers to the syndrome of a destructive, inflammatory process that leads to long standing pancreatic injury.[1]

The spectrum of chronic pancreatitis in India is variable. There are a number of studies on profile of chronic pancreatitis in south India.[2-5] The clinical spectrum of chronic calcific pancreatitis has been found to be different in northern India.[6] The aim of the present study was to delineate the clinical profile of patients of chronic pancreatitis at a tertiary care center in north India.

Material and methods

This article summarizes the profile of 103 patients which chronic pancreatitis seen in the Gastroenterology–Unit I services at PGIMER, Chandigarh from June 1999 to June 2004. Patient data was recorded prospectively in a pre-designed proforma. Data included both indoor and outdoor patients. The diagnosis of chronic pancreatitis was based on clinical, biochemical and radiological investigations.

Results

Epidemiology: Our patients hailed from adjoining states of Chandigarh. Many of these patients were referred for possible pancreatic endotherapy. 78/103 patients were male. Mean age of patients was 36.71 $\pm$ 12.94 years (Range 7-69 years). Duration of symptoms ranged from 2 weeks to 180 months (Median = 24 months).

Etiology: Etiology of chronic pancreatitis is presented in Table 1.Idiopathic pancreatitis formed the commonest etiological group, followed by alcoholism. Pancreas divisum alone was seen in 17 patients and 3 had had both alcoholism and pancreas divisum. Pancreatic calcification was evident in 50 /103 cases (48.5%). Twenty two out of 43 cases with idiopathic pancreatitis (51.1%) had pancreatic calcification.

Clinical features: These are presented in Table 2. Pain was the dominant symptom, present in 95% of cases. Among 5 patients without pain, 2 presented with upper gastrointestinal bleed, 1 each had symptoms of hyperglycemia, pleural effusion and dyspepsia. Overall, GI bleed occurred in 4 patients; 3 had bleeding from gastric varices and 1 had pseudoaneurysm of splenic artery. Jaundice was present in 11 patients. Palpable lump was present in 9 patients and all of them had pancreatic pseudocyst. Other clinical details are summarized in tables 3 and 4.

Complications: Various local and systemic complications were recorded as shown in figure 1. Pseudocyst was the commonest local complication (N=32), followed by segmental portal hypertension (11 patients).

Among diabetic patients (N=19), 14 either had symptoms of hyperglycemia, or were already on antidiabetic drugs. The remaining 5 patients were found to have abnormal Glucose Tolerance Test (GTT) or FBS. One patient of calcific pancreatitis presented with diabetic ketoacidosis after pancreatic duct stenting.[7] Seven patients out of 22 (31.8 %) had fecal fat > 7 g /day and 2 patient had symptom of steatorrhea. Three patients had biliary stricture and one developed carcinoma of the pancreas during follow up.

Management: Majority (n=78) of symptomatic patients with pain or pseudocysts, and all cases of pancreatic ascites and pleural effusion, were managed by pancreatic endotherapy. Endotherapy was technically successful in 2 out of the 78 patients. Eventually 5 of 19 (26.3%) subjects with diabetes were on diet alone and 10 (52.7%) required insulin. The remaining diabetic subjects were treated with oral hypoglycaemia drugs. Patients were referred for surgery only if there was failure to do endotherapic procedure or persistence of symptoms despite pancreatic endotherapy and maximal medical therapy. Overall 18 (17.4%) patients required surgical intervention.

Discussion

It is often difficult to differentiate recurrent acute pancreatitis from exacerbations of chronic pancreatitis. Even today, in certain situations, the correct diagnosis can often be achieved only on follow up of the patient.[8] In all our patients the diagnosis of chronic pancreatitis was confirmed by imaging studies.

As published in an earlier study from our institute[9], idiopathic pancreatitis is still the leading etiology (41.8%), followed by alcoholism (34.9%). Alcohol intake is quite common in this region of the country, and all cases of pancreatitis due to alcohol were seen in men. However 37.2 % of idiopathic pancreatitis occurred in females. Calcification was present in 51.1% of the idiopathic group and 38.8% of alcoholic patients.

Majority of patients (95.1%) had pain; however this could reflect selection bias as most patients with persistent pain were referred to our clinic. Diabetes mellitus was significantly more common in calcific pancreatitis group as compared to the non-calcific group. This may reflect that calcification develops in late stages of chronic pancreatitis associated with advanced endocrine deficiency. Patients with alcoholic pancreatitis had significantly shorter duration of symptoms as compared to idiopathic pancreatitis.

Endoscopic retrograde pancreatography followed by pancreatic endotherapy was the primary therapy in most patients. Endotherapy was done via transpapillary route in all these patients with either a pancreatic stent or nasopancreatic drain. Extra corporeal shock wave lithotripsy fragmentation of pancreatic duct calculi in conjunction with endoscopic clearance of the main pancreatic duct is associated with significant improvement in clinical outcomes in most patients with chronic pancreatitis.[10] Pancreatic stone lithotripsy was done in 7 of our patients. Surgery was done only in cases not responding to other means or when endotherapy could not be done.

To conclude idiopathic pancreatitis is the most common form of chrome pancreatitis seen at our center, and in general, the majority of these subjects showed a good respence to endotherapy

Table 1: Etiology of chronic pancreatitis in 103 patients

Etiology	N (%)
Idiopathic	43 (41.8)
Alcoholism	36 (34.9)
Pancreas Divisum	17 (16.5)
Alcoholism + Pancreas divisum	3 (2.9)
Hyperparathyroidism	4 (3.9)

Table 2: Presenting features

Clinical features	N (%)
Pain	98 (95.1)
Diabetes	19 (18.4)
Jaundice	11 (10.7)
Lump	9 (8.7)
Diarrhoea	7 (6.8)
Vomiting	6 (6.8)
G I bleed	4 (3.9)
Hyperparathyroidism	4 (3.9)

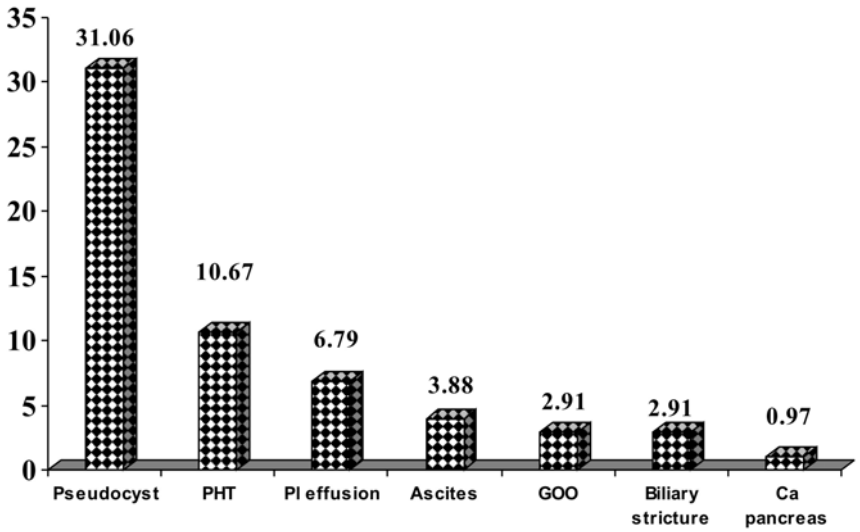
Table 3: Comparison of calcific and non-calcific chronic pancreatitis

	Calcific (N=50)	Non calcific (N=53)	p
Age	**37.0 ± 12.7**	**36.4 ± 13.2 yrs**	**NS**
Male: Female	38:12	40: 13	NS
Duration of symptoms (months .*Mean±S.D.*)	39.07 ± 38.65	40.44 ± 41.45	NS
S.amylase (SU)	205.47 ± 53.42	266.25 ± 170.68	NS
Fecal fat > 7 gm/d	6 (N=13)	1(N=9)	NS
Clinical features			
Pain	47	51	NS
Jaundice	8	3	NS
Diarrhoea	4	3	NS
Lump	3	6	NS
Vomiting	4	2	NS
GI bleed	2	2	NS
Diabetes	12	7	< 0.05
Symptomatic	10	4	0.05
Abn GTT/FBS	2	3	NS
Complications			
Ascites	1	3	NS
Pl effusion	3	4	NS
PHT	5	6	NS
Pseudocyst	15	17	NS
GOO	1	2	NS
Management			
ERCP	36	42	NS
EndoRx	33	38	NS
Surgery	12	6	NS

Table 4: Comparison of alcoholic and idiopathic chronic pancreatitis

	Alcoholic (N=36)	Idiopathic (N=43)	p
Age (years) mean+SD	**39.3 ± 11.6**	**34.4 ± 13.3**	**NS**
Male: Female	36:0	27: 16	0.0001
Duration of symptoms (Mean±S.D.) Months	22.55 ± 22.52	50.62±46.71	0.0014
S.amylase (SU) (Mean ± S.D.)	226.41±107.26	260.82±213.64	NS
Fecal fat > 7 gm/d	3 (N=8)	3(N=12)	NS
Clinical features			
Pain	33	41	NS
Jaundice	4	6	NS
Diarrhoea	3	3	NS
Lump	4	2	NS
Vomiting	2	3	NS
GI bleed	1	1	NS
Diabetes	9	8	NS
Symptomatic	5	7	NS
Abn GTT/FBS	4	1	NS
Complications			
Ascites	2	1	NS
Pl effusion	5	2	NS
PHT	5	4	NS
Pseudocyst	14	13	NS
GOO	1	1	NS
Management			
ERCP	25	33	NS
EndoRx	22	32	NS
Surgery	7	8	NS

Fig. 1: Complications of chronic pancreatitis.



References

1. Etemad Bebak and Whitcomb David C. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001;120: 682-707.

2. Balaji LN, Tandon RK, Tandon BN, Banks PA.Prevalence and clinical features of chronic pancreatitis in southern India. Int J Pancreatol 1994; 15: 29-34.

3. Chari ST, Mohan V, Jayanthi V, Snehalatha C, Malathi S, Viswanathan M, Madanagopalan N. Comparative study of the clinical profiles of alcoholic chronic pancreatitis and tropical chronic pancreatitis in Tamil Nadu, south India. Pancreas 1992; 7: 52-8.

4. Balakrishnan V, Sauniere JF, Hariharan M, Sarles H. Diet, pancreatic function, and chronic pancreatitis in south India and France. Pancreas 1988; 3:30-5.

5. Mori M, Hariharan M, Anandakumar M, Tsutsumi M, Ishikawa O, Konishi Y, Chellam VG, John M, Praseeda I, Priya R, Narendranathan M. A case-control study on risk factors for pancreatic diseases in Kerala, India. Hepatogastroenterology 1999; 46: 25-30.

6. Rai RR, Acharya SK, Nundy S, Vashisht S, Tandon RK. Chronic calcific pancreatitis: clinical profile in northern India. Gastroenterol Jpn 1988; 23: 195-200.

7. Bhasin DK, Sidhu RS, Bhansali A, Nagi B. Diabetic ketoacidosis in a patient with chronic calcific pancreatitis after minor papilla stent insertion. Gastrointest Endosc 2004; 59: 440-3.

8. Talamini G, Falconi M, Bassi C, Mastromauro M, Salvia R. Chronic Pancreatitis: Relation to Acute Pancreatitis and Cancer. J Pancreas 2000; 1(Suppl.): 69-76.

9. Kaushik SP, Vohra R, Verma R. Spectrum of pancreatitis at Chandigarh. A ten years experience. Indian J Gastroenterol 1983; 2: 9-11.

10. Kozarek RA, Brandabur JJ, Ball TJ, Gluck M, Patterson DJ, Attia F, France R, Traverso LW, Koslowski P, Gibbons RP. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc 2002; 56: 496-500.

Chapter 6

Chronic pancreatitis: Epidemiological and clinical spectrum in Jaipur

Ramesh Roop Rai, Manish Tandon, Mukul Rastogi, Nijhawan S

Summary

The spectrum of chronic pancreatitis as seen in our center shows that the main etiological agent is alcohol consumption. The disease is fairly common in North India too. An objective assessment of pain was observed to be useful in the evaluation of the patients before electing a particular therapeutic modality.

Introduction

Chronic pancreatitis is a prevalent and debilitating disease, which affects the patients mostly in their productive years of life. Pain is usually the most frequent complaint with which most of these patients present. The loss of endocrine and exocrine function which gradually develops, leads to symptoms like weight loss, anorexia, steatorrhoea and symptoms of diabetes. During the period of 2002 -2004, 126 patients with chronic pancreatitis were admitted to gastroenterology department of SMS medical college. Diagnosis was based on typical symptoms, presentations, biochemical abnormalities ultrasonography, and CT and MRCP findings. The demographic pattern of these patients is shown in Table 1. Most of our patients were in the age range of 21 to 50 years. The youngest patient was of 8-year-old male. There were 90 % male and 10 % female.

Table 1: Demographic profile

Age (Years)	No of patients
<10	3
11-20	15
21-30	16
31-40	39
41-50	36
51-60	12
>60	5
Total	**126**

Etiology

The etiological workup revealed that 75 patients (51%) had history of consumption of significant amount of alcohol for more than 7 years. Forty-five (60%) of these had concomitant history of heavy smoking along with alcohol intake. They have been smoking bidi / cigarette / hookah / cigar > 20 per day. Twenty-two (17.4%) had evidence of presence of calcification in the main pancreatic duct region as seen on the plain x-ray film of abdomen.None of these persons have been consuming alcohol or have been consuming cassava / or have been residing in Kerala. These were labeled as patients of tropical calcific pancreatitis. Five out of 126 (3.9%) patients presented with features of chronic pancreatitis, and history of pancreatitis in one or more family members. Two were twins – who had been having recurrent severe pains for more than 3 years. Two others were brother and sister. One patient had a brother, who had chronic pancreatitis, and had died. They were labelled as hereditary pancreatitis. They didn't have any other recognizable etiological factor, which could be incriminated for the chronic pancreatitis. Six out of 126 patients (4.7%) had hypertriglyceridemia. There was no other recognizable cause for chronic pancreatitis.

There were thirteen patients who had intermittent severe pancreatic type pain with mild rise of serum amylase / lipase. They had history of intake of opium for more than 10 years. These patients, on investigation, were found to have dilatation of both main pancreatic duct and common bile duct with narrowing and spasm of sphincter of Oddi. Five patients had history of blunt injury abdomen. They were labelled as traumatic pancreatitis.

Table 2: Risk factor profile

Etiology	No. of patients	%
Alcohol	75	59.5
Hereditary	05	3.9
Hypertriglyceridemia	06	4.7
Idiopathic	22	17.4
Opium addict (SOD)	13	10.3
Traumatic	05	3.9
Total	126	100

Socio-economic status

Most of our patients were from lower socio economic status, 78 out of 126 (61.9%) were from low income group. 39 patients (30.9%) were from middle-income group. Only 9 (7.2%) were from high socio economic group. This could be bias due to referral anomaly. Most of our patients are from lower socio economic strata, possibly because our center is a government medical college and hospital which caters to people from this strata.

Table 3: Socioeconomic status

Socioeconomic status	No of patients	%
HIG	09	07.2
MIG	39	30.9
LIG	78	61.9
Total	126	100

Clinical profile

All the 126 patients presented with the chief complaint of abdominal pain. The pain characteristics varied from severe excruciating pain anteriorly above the umbilicus, to pain correspondingly in the back only. This affected their quality of life. Twenty patients (63%) developed loss of appetite; of these 20% had fear of development of pain if they had food and consequently developed loss of weight. Others had loss of appetite due to the disease process. None of the patients had significant steatorrhoea. Thirty patients (25%) had lump in the abdomen, due to pancreatic pseudo cyst. Fifteen of these patients had impression in the stomach and endoscopic cystogastrostomy could be performed successfully. Five of the remaining were drained with ultrasound guidance. The other 10 were followed up as they did not have any compressive symptoms demanding any drainage procedure. Twenty four patients (20%) had diabetes mellitus. Fifteen patients had tropical calcific pancreatitis. Eight had history of calcification due to chronic alcoholic pancreatitis. All of them needed injection insulin to control the elevated blood glucose levels.

Twelve patients had jaundice secondary to CBD stricture due to chronic pancreatitis. Nine (8%) had pancreatic ascites. Two patients, in whom it was significant, responded to subcutaneous octreotide treatment.

Table 4: Clinical problems encountered

Sign and symptoms	No of patients	%
Pain	126	100
Ascites	9	8
Diabetes	24	20
Weight loss	63	50
Lump abdomen	30	25
Jaundice	12	10
Steatorrhoea	0	0

Assessment of pain

In most of the clinical situations, the intensity of the pain was assessed on visual analogue scale - either 0 to 10 or 0 to 100 scale. This encompasses only the intensity, which is based on subjective feeling. To add objectivity to the intensity of pain, its frequency and its consequence, a scoring system was used to grade the pain. Its intensity (I) frequency (F) and consequences (C) were assessed at every visit to determine a "pain score". Intensity (I) was given a score of 0 to 8 on the following scale.

Frequency (F) and Consequences (C) were also assigned maximum scores of 8 each, but the latter were made up of 4 score of two different subcategories. Thus the 8 scores of F were made up by 4 scores of pain episodes / year and 4 of duration / year as shown below. Similarly C was assessed by two different parameters each comprising a maximum score of 4.

The maximum score possible of I, F and C together was thus 24. Depending on the sum of the three sets of scores (I, F and C) for an individual patient, he / she was categorized as having: mild

(scores 1-8), moderate (scores 9-14) or severe (score 15-24) pain. The pain score was developed to take into consideration not only the pain severity on visual analog scale, but also other parameters like frequency of pain episodes per year and duration of pain in hours per episodes, consequences leading to work loss in months per year and number of hospitalizations per year. Pain score helped in selecting patients for specific therapeutic interventions in the form of pancreatic stenting, epidural block or surgery to alleviate the pain. Assessment of all above parameters was useful in evaluating the affect of therapeutic interventions pre and post intervention.

The present appraisal from a tertiary care hospital shows that chronic pancreatitis is a common disorder. Alcohol is the main etiological agent. Fairly large numbers of patients with tropical calcific pancreatitis are observed in northern India also. An objective assessment of pain was observed to be useful in the evaluation of the patients before electing a particular therapeutic modality.

Box 1: Assessing the severity of pain

Grade	Variable
No pain	I-0
Insignificant pain (only on direct questioning)	I-2
Mild pain	I-4
Moderate pain (analgesics regularly required but no drug dependency)	I-6
Severe pain (drug dependency present and sleep disturbed regularly)	I-8

Box 2: Scoring the frequency/consequences of pain

Score	0	1	2	3	4
(F) **Frequency**					
Of pain episodes / year	3	4-6	7-9	10-12	12
Duration in hrs / episode	< 12	12-24	24-28	48-78	72
(C) **Consequence**					
Work loss in months / year	0	1	2-4	5-8	8
No. of hospitalizations / year	0	4	5-8	9-12	12

Table 5: Pain score of patients in the present study

Pain Score		No of patients	%
1 – 8	Mild	25	20
9 – 14	Moderate	25	20
15 – 24	Severe	76	60
Total		126	100

Table 6: Diagnostic imaging in the present series

Investigations and finding X ray abdomen	No. of patients
* Parenchymal	3
* Ductal	
Site of calcification	
Head alone	21
Head and body	3
Body	4
Body and tail	4
Whole MPD	2
USG Abdomen	126
MPD Dilatation	60
Tropical	22
Opium	13
Alcohol related	25
MPD calcification	34
Parenchymal calcification	3
Pseudocyst	24
CECT	60
MPD Dilatation	35
Calcification	
Ductal	34
Parenchymal	4(one more than USG)
MRCP	10
MPD Dilatation	10
ERCP	75
Pancreatic ductal calculi	34
Dilated and tortuous MPD	55

Reference

1. Chronic calcific pancreatitis: Clinical profile in northern India. RR Rai, SK Acharya, S Nandy, S Vashisht and RK Tandon. Gastroenterology Japonica 1988: 23 (2); 195-96

Chapter 7

Chronic pancreatitis in Orissa

Shivaram Prasad Singh

Summary

In Orissa, experience with chronic pancreatitis is shared between the gastroenterologist and the endocrinologist. However, exciting work is in progress to unravel the basis of this illness, and we discuss the results from autoantibody testing, HLA-linked susceptibility studies as well as SPINK-1 mutations amongst subjects with this illness. In addition, we also summarize unusual presentations of the disease and our experience with ultrasound assessment in this setting.

Introduction

Any discussion on chronic pancreatitis (CP) in Orissa, especially tropical calcific pancreatitis (TCP) brings to mind the verses of The Blind Men and the Elephant written by John Godfrey Saxe. The story of tropical pancreatitis in Orissa is a tale of two departments. The clinical features of tropical pancreatitis as presented and published from the two departments – endocrinology and gastroenterology are totally at variance.

Etiology of chronic pancreatitis in Orissa:

The majority of cases of CP in Orissa are due to tropical calcific pancreatitis (TCP). Alcoholic pancreatitis is very uncommon in Orissa; it constitutes only 10% of all cases of CP seen in Orissa. Tropical calcific pancreatitis (TCP) is a chronic pancreatitis unique to developing countries in tropical regions. The cause of TCP is obscure. Whereas environmental factors such as protein energy malnutrition and ingestion of cassava have been implicated, a genetic predisposition to the disease also may be important.

Cassava and CP in Orissa

Heavy consumption of cassava has been implicated in the etiopathogenesis of tropical pancreatitis in Kerala. However, cassava is seldom consumed in Orissa, except in some pockets in coastal southern Orissa. However, paradoxically, TCP is seldom reported from this part of Orissa. Most patients hail from the eastern coastal region, although it is also seen in western Orissa.

Malnutrition

Besides, there is insufficient evidence to implicate protein and energy malnutrition in the causation of tropical pancreatitis. However, Tripathy et al found that 85% of the FCPD (Fibrocalculous pancreatic diabetes) patients hail from areas of predominantly low or very low socioeconomic status. History of alcoholism was not found in a single case.

Alcohol and chronic pancreatitis in Orissa

Alcohol is responsible for about 10% of cases of CP in Orissa today. This is in contrast to the scenario two decades ago when history of significant alcohol intake was not present in a single case of a published series of CP. With increasing industrialization and increase in alcohol consumption, the frequency of alcoholic pancreatitis is going to increase, as we are seeing a surge in the cases of alcohol related acute pancreatitis getting admitted to the medical wards.

Autoimmunity and chronic pancreatitis in Orissa

The prevalence of GAD65 antibodies was studied in 46 FCPD patients of Orissa by Kanungo and associates, and they found that none of the FCPD patients were positive for GAD65 antibodies. In contrast, autoantibody frequency was 4% in healthy controls, 49% in type 1 DM patients, 32% in PDDM patients, and 42% in type 2 DM patients. This suggests that autoimmunity does not have any role in the etiopathogenesis of FCPD in Orissa.

HLA Class II gene polymorphism

There is limited data from genetic studies of malnutrition related diabetes. HLA class II gene polymorphism were analyzed in different types of diabetes mellitus patients from Cuttack, and an association of DQ9 with FCPD was found; FCPD was positively associated with DQ9 (A*0201-B*0303). The investigators suggested that there were differences in the genetic background for susceptibility between type 1 DM and MRDM in the Cuttack population.

SPINK1 gene mutation

As a modifier role has been proposed for trypsin inhibitor (serine protease inhibitor, Kazal type I; SPINK1) mutations, the role of SPINK1 mutations in TCP patients of Orissa is also being analysed. We are investigating SPINK1 gene mutation in both tropical calcific pancreatitis patients and controls. The frequency of N34S in SPINK1 was studied in 20 patients and was found to be 55%; in controls it was 2.3%, not too different from what has been reported in other studies. The mother of a girl with chronic calculous pancreatitis had shrunken hyperechoic pancreas with a dilated pancreatic duct and the mother was diabetic too. Both the mother and daughter had mutated *SPINK1*. These data suggest a common genetic basis for tropical calcific pancreatitis with additional genetic/environmental factors responsible for the variability of phenotype as has been speculated in other similar studies.

Clinical features of chronic pancreatitis in Orissa

The profile of clinical features of chronic pancreatitis in Orissa depends upon the subset of patients who are seen by the reporting investigator. The earlier picture based on FCPD patients presenting predominantly with diabetes mellitus to the physicians or diabetologists was quite different from that of the patients consulting the gastroenterologists for pain. Analysis of two decades old data on pancreatic diabetes patients admitted to the medical and endocrinology wards reveals that the incidence of pancreatic diabetes among all diabetics admitted to the medical wards was 3.7% and among young diabetics below 40 and 35 years 9.8% to 11.7% respectively. Most of these patients with pancreatic diabetes (74%) were between age ranges of 10-30 years. Most (88%) of the patients belonged to poor or very poor socioeconomic status. The nutritional status was poor in the majority of patients; about 90% of the patients were underweight and clinical signs of malnutrition were seen in about 40% patients. Family history was positive in less than 10% of cases. History of abdominal pain, often elicited by direct questioning, was elicited in 42% patients. Pain was rare as a presenting feature among the diabetics. Most of the patients had severe diabetes with gross hyperglycemia. However, it has been observed that after surgery, there is not only remarkable amelioration of the symptoms,

improvement in nutrition and quality of life, but also that the insulin requirement is reduced. Uncommonly, the patient does not require insulin after surgery. The presenting features of these patients with FCPD are as shown in Table 1.

Table 1: Presenting features of FCPD patients in Orissa

Weakness (asthenia)	100%	Fatty stools	24%
Thirst (polydipsia)	80%	Ketosis	16%
Abdominal pain	42%	Infection	16%
Neuropathy	45%	Gallstones	6%
Parotid enlargement	30%	Retinopathy	4%

Although at one time it was difficult to think of a patient with chronic pancreatitis without pain, the position now is quite different; a good number of patients with chronic pancreatitis particularly patients with diabetes mellitus have no pain. Interestingly, early studies from Cuttack[6] found severe pain in only 12% patients; this was similar to the 10% pain prevalence reported from Diabetes Research Centre, Chennai. It is important to note here that these data pertain to FCPD patients presenting with diabetes mellitus. These figures often gave a wrong impression that tropical calcific pancreatitis in Orissa was generally painless. On the contrary, the prevalence of pain as a presenting feature in TCP patients attending the gastroenterology department is 79%, which is similar to the pain prevalence reported from Trivandrum (82%).[8]

The clinical profile of TCP patients attending the gastroenterology outpatient department is quite different from that of the FCPD patients. The clinical profile of TCP patients attending a gastroenterology clinic is shown in Table 2.

Table 2: Clinical profile of TCP patients in the gastroenterology clinic

Male : female	2:1
Age below 35	75%
Poor nutrition	33%
Overt diabetes	25%
Pancreatic pain	79%
Fatty stool	12%
Pancreatic cancer	2 cases

TCP today, is not as formidable a disease as it used to be considered, thanks to better diabetic care and management of complications. Patients of TCP from the better socio-economic status have now a much better prognosis than earlier.

Tropical pancreatitis and pancreatic carcinoma in Orissa

Pancreatic carcinoma is believed to be a dreaded complication of TCP and published literature would make us believe that patients with TCP are at least 8 times more likely to develop carcinoma than controls. Indeed, TCP is considered by many as a premalignant disease. An analysis was undertaken to study the association of pancreatic carcinoma with TCP in Orissa. This involved 499 patients studied and followed up over a period of two decades from 1975 to 1995. Diagnosis of TCP was made by X-ray and/or ultrasonography. These patients were followed up at intervals varying from 6 to 12 months for a mean period of 8.2 years. Ultrasound was performed at intervals of 12 to 24 months in 312 patients to study the pancreatic morphology and to detect the development of malignancy. Surprisingly none of the patients developed pancreatic carcinoma during follow up. However, during the same period, 10 new patients with pancreatic carcinoma were seen and two of them had pancreatic calculi.

It is concluded that contrary to what has been reported from other parts of the country, patients with TCP did not have an increased predilection for pancreatic carcinoma in this part of the country. However, this issue needs to be carefully examined. Two questions need to be answered: what is the true frequency of pancreatic malignancy in these patients? Does surgery alter the predisposition to malignancy? Data from published literature are inadequate and prospective studies are needed.

Unusual presentations

There were two unusual presentations that are worth mentioning. One of our patients presented with hemetemesis and melena; he gave recurrent history of abdominal pain suggestive of pancreatitis and gastroscopy revealed fundal varices as the source of bleed. Ultrasonography revealed chronic calcific pancreatitis with splenic vein occlusion.

About 5% patients presented with cholestatic jaundice due to ampullary obstruction by pancreatic calculi. In one of the patients, biliary dilatation and jaundice resolved after spontaneous passage of the stone across the ampulla into the duodenum. In another patient, relief was obtained after endoscopic removal of the stone. Most of these patients more the less required subjected to surgery.

Ultrasonography and TCP

Ultrasound can pick up a good number of cases missed on routine plain X-ray of the abdomen. In about 50% of the cases in whom diagnosis was made by sonography, plain X-ray of the abdomen missed the calculi. With ultrasonography increasing number of patients with this disease are picked up early even before conventional X-rays can detect calculi/ calcification. Increasing referrals for ultrasonography has resulted in increased detection of TCP. In the pediatric age group too, thanks to sonography, a fair number of patients who were earlier treated for parasitosis or unexplained recurrent abdominal pain have been diagnosed to be suffering from TCP. This has resulted in a relative increase in detection of patients presenting predominantly with pain.

Twenty-four patients who were initially diagnosed as PDDM, with X rays negative for calcification, revealed calculi when ultrasonography was done. (Table-3) and about half of them (45%) complained of abdominal pain. Thus, there may be an overlap between cases of PDDM and FCPD. None of these patients had ever consumed alcohol. It is difficult to classify some of these patients. The daughter of one of these patients had chronic calcific pancreatitis with pain and a markedly dilated main duct, necessitating surgery, but did not have diabetes mellitus.

Table 3: Observations from an ultrasonographic study of 108 patients

Group-I (77.8%)	No pancreatic abnormality on ultrasonography.
Group-II(14.8%)	Shrunken irregular hyperechoic pancreas with dilated irregular PD, but no stones/calcifications. Pain was present in 44%.
Group-III(7.4%)	Shrunken irregular hyperechoic pancreas with bright echogenic areas & irregular dilated PD without stones, pain was present in 50%.

In the light of our clinical and ultrasonographic data, we feel there is a definite need for a reappraisal of the definition of chronic calcific pancreatitis of the tropics. It would be interesting to look for SPINK1 gene mutation in these patients.

Conclusion

Very little progress has been made in our knowledge of the etiology of TCP. It is time there should be a combined multi-disciplinary approach by clinicians, radiologists, endocrinologists, therapeutic endoscopists and surgeons if we are to unravel the mysteries of this enigmatic disease and optimize therapy for patients

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Reference

1. Sanjeevi CB, Kanungo A, Shtauvere A, Samal KC, Tripathi BB. Association of HLA class II alleles with different subgroups of diabetes mellitus in Eastern India identify different associations with IDDM and malnutrition-related diabetes. Tissue Antigens 1999;54:83-7.

Chapter 8

Profile of chronic pancreatitis in North Kerala – A retrospective descriptive study

Varghese Thomas, Harish K

Summary

Chronic calcific pancreatitis is a disease initially described in the middle and southern parts of Kerala. We describe our experience with chronic pancreatitis from North Kerala. Pain was the commonest presenting symptom. A minority, nevertheless a significant proportion (29%) of our subjects, consumed cassava. Recurrent hypoglycemia was the most common metabolic complication in these subjects. We also suggest that further studies be conducted to determine the link between chronic pancreatitis and low intake of vegetables/fruits.

Introduction

In Kerala, chronic calcific pancreatitis (CCP) has been considered as a disease of middle and southern parts of the state. There are only a few cases of chronic pancreatitis described from north Kerala so far. The present study aims to present the epidemiological and clinical data of patients with CCP seen in a tertiary care in north Kerala over the past two decades.

Materials and methods

Patients with chronic pancreatitis who were attending the departments of gastroenterology, medicine, surgery and the diabetic clinic of Medical College, Calicut were included in the study for a period from 1982-2004. Chronic calcific pancreatitis is defined for the purpose of this study as any patient with radiological / ultrasonologic/ CT scan/ ERCP evidence of pancreatic parenchymal calcification or ductal calcification. Inclusion criteria: Patients above the age of 12 years with chronic calcific pancreatitis (patient with radiological / ultrasonologic/ CT scan/ ERCP evidence of either pancreatic parenchymal or ductal calcification.).

Exclusion criteria

Definite evidence of hyperparathyroidism, patients with pancreatic diabetes without evidence of pancreatic calcification and definite evidence of hereditary pancreatitis. Subjects and sample size: 230 patients above the age of 12 years seen in outpatient and inpatient departments of gastroenterology, medicine, surgery and the diabetic clinic of Medical College Hospital, Calicut during the study period November 1982 to November 2004 with a diagnosis of chronic calcific

pancreatitis were included in this study.The study on profile of patients with chronic pancreatitis was a departmental objective from 1982 onwards and a standard proforma was used to collect data whenever a patient with chronic pancreatitis was seen by any member of the department. All demographic, clinical and investigation details were entered in the proforma and periodically updated as and when patients returned to our department. Between May 1996 and April 1998, the diet history a group of 31 patients were studied in detail with special reference to cassava intake.Tropical calcific pancreatitis (TCP) was diagnosed only after exclusion of indulgence in alcohol. Alcoholic chronic pancreatitis (ACP) was diagnosed in patients having a long history of significant alcohol consumption either on a daily basis or several times per week (exceeding 80g/day).

Results

General observations

A total of 230 patients with chronic calcific pancreatitis were included in this study. Two hundred and seven patients satisfied the criteria for inclusion in the TCP group. The geographical location of these patients is given in Table1. The age, sex and religion wise distribution of patients with chronic pancreatitis is given in Table 2. Tables 3 to 5 describe the clinical, radiological and calculi-related features of the patients.

Table 1: Geographical location

District	Number	(%)
Kozhikode-urban	27	13
Kozhikode-rural	74	35.7
Malappuram	45	21.7
Kannur	21	10
Palakkad	12	5.8
Thrissur	6	2.9
Wyanad	6	2.9
Kottayam	4	1.9
Kasargod	3	1.4
Miscellaneous	9	4.3
Total	**207**	

Table 2: Age, sex, religion of 230 cases of chronic pancreatitis

	Alcoholic calcific pancreatitis	Tropical calcific pancreatitis
Number of patients	23	207
Male : Female	23:0	148: 59 (ratio – 2.2 : 1)
Hindu	19 (83 %)	129 (62.3%)
Muslim	1 (4.3 %)	67 (32.4 %)
Christian	3 (13 %)	11 (5.3 %)
Mean age of onset of symptoms (range)	47.2 yr (23-71)	35.7yr (9-65)

Table 3: Presenting symptoms in TCP

Symptoms	No. of cases (Total 207)
Abdominal pain	98 (47.34%)
Diabetes mellitus	74 (35.7 %)
Steatorrhoea	23 (11.1%)
Jaundice	12 (5.8%)

Table 4: Radiological investigations
(CT scan / Ultrasonogram / plain x-ray of abdomen))

Abnormalities	No. of cases 207	
Dilated main pancreatic duct	56	27 %
Psuedocyst	44	21.3%
Dilated biliary system	10	4.8%
Ascites	9	4.3%
Mass head of pancreas	6	2.9%
Pancreatic calcification	204	
Equivocal findings	3	

Table 5: Size of pancreatic calculi on plain x-ray of abdomen (48 cases)

Size of calculi	ACP n =17	TCP n = 31
>1cm	2 (11.76%)	20 (64.51 %)
0.5-1cm	7 (41.17%)	9 (29%)
<0.5 cm	8 (47%)	2 (6.45)

Complications

Ten patients with TCP presented with obstructive jaundice and 6 were found to have mass lesion in the region of head of pancreas (2.9%) and four patients had benign stricture of lower end of bile duct. Pseudocyst of pancreas was seen in 44 patients (21.3%) with TCP in comparison with 8 patients with ACP (34.7%). Pancreatic ascites was seen in 9 patients with TCP (4.3%). The pain became intractable in 13 (6.28 %) patients and they were subjected to surgical procedures. Severe protein calorie malnutrition with kwashiorkor like skin changes were observed in one patient (14 years) who also had evidence of a large pseudocyst. (Fig 1)

Familial clustering

Presence of TCP in other members of the family was observed in 4 patients (2 siblings, and 2 identical twins).

Cassava consumption and alcohol intake

Detailed diet history was obtained from 31 patients with TCP. History of daily consumption of cooked cassava was obtained in 9 patients (29%). The mean daily cassava intake was 222.22g (range 100 to 500 g) for a mean duration of 12 years (range 7 – 12). In 11 (35.8%) patients, the mean cassava intake was 126 g weekly and 11 patients never had taken cassava (35.48%). The mean daily intake of vegetables in these patients were 20 g/day. The mean calorie intake was 1830 kcl/day.

Three patients with TCP with long history of abdominal pain and diabetes mellitus in young age also gave a history of significant alcohol intake.

They had noticed symptoms of pancreatitis much before they took to the habit of regular alcohol intake. The mean alcohol intake in 23 ACP patients were 141.1 g per day and the mean duration was 19 years (range14-30 years)

Discussion

Ninety percent of subjects in our group belonged to the category of TCP and only 10% belonged to the ACP group. All patients in ACP group were males and 83% of patients were Hindus where as only 4 % of the ACP patients belonged to the Muslim community. The low occurrence of ACP among muslim patients may be due to the low prevalence of alcoholism in that community. Among the 207 patients with TCP, the male : female ratio was 2.2: 1. Various other studies [1,2] indicated male preponderance of 1.63 - 3: 1 but a field study [3] in 1988 revealed higher incidence among females, M: F – 5:8.

Forty nine percent of our patients with TCP belonged to Kozhikode district, 35.7 % to Kannur District and 21.7 % belonged to the Malappuram District. Overall 167 patients from these three adjacent districts together contributed to 81% of cases of TCP. It is intriguing to note that only 3% of patients belonged to the Wyanad district with geographical features and dietary habits similar to the Kottayam District in middle Kerala where the disease was described in large numbers earlier by Geevarghese[1]. It is all the more interesting to note that large number of people belonging to the Wynad district are either migrants or descendants of migrants from the same belt in middle Kerala where TCP was noted in large numbers earlier. In our study, there were only 4 migrants from Kottayam District who had settled in north Kerala during their childhood days.

One previous study[4] has pointed out about the occurrence of pancreatitis in Calicut region and it was stated that the disease is more common in the migrants from central Kerala. However, our present study clearly showed that TCP is prevalent more in the native population of north Kerala than in the migrants from central Kerala region who had settled predominantly in Wynad District. The religion wise distribution of patients roughly corresponded to the census data of religions. Less

number of cases are reported from the northern most district of Kasargod, which could to due to the proximity with Manipal, where Kasturba Medical College is situated.

Classically, a vast majority of cases with TCP are diagnosed between 11 and 30 years of age. The remaining cases are detected in the fourth decade[5, 6]. The mean age at onset of symptoms in our study was 35.37 years with a range of 9 to 65 years. Eighty-seven patients (42%) were found to be above 40 years, compared with 3.25%, 7.25%, 16.4 % and 33 % above 40 years age reported from south Kerala, Madras, Pune and Central Kerala respectively.

The mean age at onset of symptoms in ACP patients in our study was 47.2 years with a range of (23-71) years. The average age of intake of alcohol was 141.17 g day and mean duration of drinking was 19.7 years with a range of 12-30 years. Various studies have shown that daily intake of 150 g alcohol for a minimum duration of 5 - 6 years is required to produce alcoholic calcific pancreatitis. Our study revealed that average intake of alcohol was almost similar to other studies, but the minimum duration of drinking was 12 years.

Among the 31 patients with TCP in whom a detailed diet history was available, only 9 patients gave a history of consumption of cooked cassava as staple diet daily, with an average intake of 222.2 g for a mean duration of 12 years. Eleven patients (35.48%) never had consumed cassava. The average daily intake of calories in these patients was 1830 kcals. Both ACP and TCP patients in our study had a predominantly rice based diet rich in carbohydrates. A study of cassava consumption in patients having TCP at Kottayam showed that the intake of cassava was 373.3g /day among those with TCP and 167.3 g among those without the disease.

Geevarghese had presented epidemiological data to suggest a positive correlation between cassava intake and incidence of TCP in several geographic areas. Cyanogenic glycosides contained in cassava are considered to be the toxic factors. Although in north Karnataka and Pune there is scope to incriminate an alternate cyanide containing staple diet (sorghum), no such factor can be suggested in Tamil Nadu, Andhra

Pradesh, Orissa and West Bengal. Tuescher et al[7] failed to find cases of TCP in a West African population with high cassava consumption. Experimental studies have not conclusively proven the role of cassava in TCP yet.

Four patients in our study had a sibling with TCP of whom two were identical twins, and another an elder brother. Fewer numbers of familial clustering may indicate that environmental factors may be playing a greater role in the causation of TCP than genetic factors.

Many of our patients belonged to the poor or lower middle class socio-economic category. There were some patients who belonged to a rich background. Over 80% of patients seen in hospitals in Trivandrum and in Cuttack were poor or very poor. However, patients with TCP detected at private or paying clinics do not belong to poor socio-economic group.

Complications of diabetes mellitus were seen in 32 out of 74 of our patients (43.2%) with TCP. Most common complication was recurrent hypoglycemia. Long-term complications of diabetes (neuropathy, myopathy, retinopathy) were noticed in 12 patients (16 %). The incidence of overt diabetes was seen in 34% of 404 ACP patients studied by Howard and Jordan [8] from 118 reports on the subject and 45% in the series of Marks and Bank from South Africa, whereas in TCP the incidence of diabetes had been reportedly quite high, even up to 90%[9].

Abdominal pain was present in 89% of our TCP patients. This is comparable with various other reported studies. Steatorrhoea as a complaint was seen in 11% of our patients with TCP. However, one study had shown that 76% of patients had steatorrhoea when a standard fecal fat estimation was done. Our patients with steatorrhoea complained of passing greasy stools and dripping of oil from anus during defecation. This description of steatorrhoea in TCP is in sharp contrast to the textbook description of steatorrhoea characterized by profuse, frothy and foul smelling stools. This specific complaint of passing of oil per anus occurs especially after a fatty meal and this is highly diagnostic of exocrine pancreatic failure. Therefore this type of steatorrhoea is to be clinically distinguished from classic steatorrhoea seen in small bowel disease, and a new term of *oilorrhoea* is proposed to be used to describe the

steatorrhoea in exocrine pancreatic dysfunction.

Ten patients in our study presented with obstructive jaundice and in 6 cases a mass was found in the head region of pancreas (2.9%). It is estimated that patients with tropical pancreatitis are at least 8 times more at risk of developing pancreatic cancer compared to controls. In a recent follow up of 266 patients with TCP studied over 8 years period in Kerala, 22 patients (8.3%) had pancreatic carcinoma and their mean age was 46.8years.

Another observation is that 64.5% of our TCP patients had calculi >1cm size where as 47% of ACP patients had calculi <0.5 cm in size in plain X ray abdomen. TCP is characterized by the frequent occurrence of large, discrete, dense calculi. Patients with alcoholic calcific pancreatitis have typically small, speckled calculi with irregular hazy margins. This finding is consistent with earlier observations by Chari et al[10]

The diagnosis of tropical pancreatitis in the absence of calcification is difficult. In our series we have not included non-calcific pancreatitis i.e. patients who are juvenile diabetics with unequivocal exocrine or morphological changes in the pancreas. This might explain the low incidence of diabetes mellitus in our series. Another observation in our series which warrant further studies is the low intake of vegetables and fruits in TCP patients.

New hypothesis

In this context it is worthwhile to explore the possibility of other environmental agents in the causation of TCP. Alcohol is a definite risk factor for chronic pancreatitis. Ethyl alcohol is produced by fermentation of carbohydrates. It has been proven beyond doubt that ethyl alcohol even though in small quantities is produced in human intestinal tract by bacterial and fungal fermentation. There are studies, which have suggested a role for endogenous alcohol in the causation of non-alcoholic steatohepatitis[r]. Both cassava and rice are rich in starch and the epidemiological association of cassava with TCP may be linked through endogenous production of alcohol like substances. It is possible that some chemicals similar to ethyl alcohol is produced by fermentation

of carbohydrates in the intestinal tract and this substance is not detoxified properly in patients with TCP which may lead to pancreatic damage. This defect in detoxification may be genetically determined. Further studies are required in this direction to prove or disprove this hypothesis

Summary

With better understanding of the illness it seems that the natural history of TCP previously described by Geevarghese as pain between the ages of 6-10 years, diabetes by the age of 20 years and death before age of 30 years had definitely changed. In north Kerala, the disease is less common in the hilly regions and the role of cassava seems to be less important. Familial clustering of TCP is infrequent in north Kerala. The search for the role of other environmental factors should continue.

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References

1. Geevarghese PJ. Epidemiology of chronic pancreatitis. In: Chronic pancreatitis in India. Balakrishnan V, Ed. Indian society of pancreatology 1987: 67- 71

2. Augustine PA. Three-year study of chronic pancreatitis in Kerala. In: chronic pancreatitis in India. Balakrishnan V, Ed. Indian society of pancreatology 1987;75-78

3. Balaji LN, Tandon RK,Tandon BN et al. Prevalance and clinical features of chronic pancreatitis in South India. *Int J Pancreatol*. 1994 Feb;15(1):29-34.

4. Meenu Hariharan. Clinical features of Tropical calcific pancreatitis. In : TCP- proceedings of the first round table conference 1994; Ed.Nirmal Kumar

5. Mohan V, Chari ST, Viswanathan M and Madanagopalan N. Tropical calcific pancreatitis in South India. Proceedings of Royal College of Physicians of Edinburgh 1991; 20:34-42

6. Tripathy BB and Samal KC. Chronic calcific pancreatitis with diabetes in the young in Orissa. In: chronic pancreatitis in India. Balakrishnan V ,Ed.Indian Society of Pancreatology 1987;89-96

7. Tuescher T, Baillod P, Rosman JB and Tuescher A. Absence of diabetes in a rural West African population with a high carbohydrate/cassava diet. *Lancet* 1987;1:765-768

8. Howard JM, Jordan GL Jr. Pancreatic calcification. In: Surgical diseases of the pancreas, Philadelphia. J.B Lippincott 1970;p203

9. Kajubi SK. A short review of pancreatic diabetes in Uganda*. East African Medical journal* 1979; 56: 625 -30

10. Chari S, Jayanthi V, Mohan V, Malathi S, Madanagopalan N, Viswanathan M et al. Radiological appearance of pancreatic calculi in tropical versus alcoholic chronic pancreatitis. J Gastroenterol Hepatol. 1992;7:42-44

Chapter 9

Tropical pancreatitis: data from Manipal

Ganesh Pai C

Summary

At the Kasturba Hospital in Manipal, tropical pancreatitis is still the commonest variety of chronic pancreatopathy. Oxidant stress plays a major role n the genesis of TP, and in our studies with curcuma curcumin, we have shown that oxidant stress-related changes are reversible. However, clinical benefits of curcumin therapy are questionable.

Introduction

At Kasturba Hospital Manipal, we see about 20 new cases of chronic pancreatitis in a year. They constitute less than 1% of patients presenting to the hospital for the first time. About 60% have tropical pancreatitis (TP) and the rest, alcoholic. Other types of chronic pancreatitis are seldom encountered. The following data pertain to 72 patients with TP (old and new cases) collected over a four year period from 1997-2000.

Age and sex patterns

The patients were aged 5 – 73 (mean 27.6) years. While the majority were younger than 41 yrs of age, it is interesting to note that 6 pts (8.3%) were older. The male to female ratio was 3.2 : 1. They had symptoms for 1 week to 20 years at the time of evaluation. The classic description provided by Geevarghese, of pain in childhood, diabetes in adolescence and death in the prime of life is rarely encountered these days.

Clinical features at presentation

Sixty-eight (94%) had abdominal pain, 27 (37.5%) had diabetes mellitus, and 17 (23.6%) had history suggestive of steatorhoea. Pancreatic calcification was seen in 45 (62.5%), pseudocysts in 9 (12.5%), bile duct strictures in 4 (5.5%), pancreatic cancer in 3 ((4.2%) and splenic vein thrombosis in 3 (4.2%). Four (5.5%) were addicted to opiates.

Treatment

We treat abdominal pain in these patients with anti-oxidants (Cap Antoxid 1 tid), and pancreatic enzymes supplementation (6-9 tablets/day)

along with analgesics as necessary. About 75 to 80 % respond. Those who do not, are treated endoscopically with stenting and spincterotomy of the pancreatic duct. Thirteen patients from the above series underwent the procedure, but the data pertaining to a longer period, is given in table 1.

Table 1: Results of endoscopic therapy in tropical pancreatitis

Evaluable patients	(n=19)	Remarks
Successful sphincterotomy +/-stenting	17 (89%)	Both = 14 Sphincterotomy only = 3
Major complication	1 (pancreatic sepsis)	Requiring stent removal
Stent free at 6 months	8	
Pain relief	14 (74%)	
Further follow-up of	6 - 20 mo	Pain relief persisted

Targeting oxidant stress

We have shown that oxidant stress occurs in patients with TP and also that treatment with curcumin (500mg), an anti-oxidant derived from turmeric, along with piperine (5mg), reverses these changes. However there was no improvement in pain in these patients. We are now investigating whether a higher dose of the drugs and more prolonged treatment could accrue clinical benefit.

Surgical therapy

Lateral pancreatico-jejunostomy was done in 6 (8.3%) of the 72 patients either because of failed endoscopic procedure or non-response. There was good response initially in 5 of these.

Tropical pancreatitis and idiopathic pancreatitis of the West

TP appears to have changed in its clinical presentation over the last few decades since the original description given by Geevarghese. Our own

data and those from elsewhere in the country on the genetic abnormalities, clinical features, and the risk of malignant transformation support this assumption and raise some interesting questions:

Is TP the same disease as the idiopathic pancreatitis of the West? If so, why does it still behave differently from the disease prevalent in the West? Could the changes in the dietary patterns that have occurred in the last few decades explain the evolution of the clinical presentation of TP seen in recent decades? With further improvement in the nutritional value of our diet and 'Westernisation' of our food habits, will TP homogenize itself into a single entity of "Idiopathic" (or distinct subgroups of genetically determined) pancreatitis?

References

1. Pai CG et al. Evidence for oxidant stress in chronic pancreatitis. Indian Journal of Gastroenterology. 1999;18:156-7.

2. Pai C G et al. Stenting of pancreatic duct and pancreatic sphincterotomy for relief of pain in tropical pancreatitis. 2004. (Manuscript under review.)

3. Pai C G et al. Anti-oxidant effect of curcumin in tropical pancreatits: a pilot study. 2004 (Manuscript under review.)

Chapter 10

Etiology and clinical profile of chronic pancreatitis – the CMC Vellore experience

Ashok Chacko, Shajan Peter

Summary

We describe the etiology, clinical profile and response of pain to therapy of patients with chronic pancreatitis seen at the Christian Medical College, Vellore. A total of 173 patients diagnosed to have chronic pancreatitis between 2000 and 2004 were included in this retrospective analysis. From the results of our study, we conclude that idiopathic chronic pancreatitis is the most common form of chronic pancreatitis seen in Bengal and Tamil Nadu. Cationic trypsinogen gene mutations were not seen in early and late onset chronic pancreatitis. Heterozygous SPINK 1 gene mutation was present in 55% of early onset chronic pancreatitis and 30% of late onset chronic pancreatitis. Homozygous SPINK 1 mutation was present in 14% of early onset of chronic pancreatitis.

Most patients presented in 2nd and 3rd decade of life. Duct disruptive complications were more often seen in alcohol-related chronic pancreatitis as compared to idiopathic chronic pancreatitis. Diabetes mellitus was present in 29% and steatorrhoea in about 10% of patients. About 78% of patients treated with enzyme supplements had partial or complete response of abdominal pain. For pain relief in chronic pancreatitis surgery was better than endotherapy in our experience.

Introduction

Idiopathic Chronic pancreatitis (Tropical chronic pancreatitis) was earlier thought to be seen only in certain areas of India. During the last few years, gastroenterologists have been detecting classical cases of idiopathic chronic pancreatitis from almost all states in the country. The clinical profile, complications and response to therapy may be different in different parts of India. It is therefore important that experiences from different parts of the country be recorded. This will become the baseline for planning future studies in chronic pancreatitis. We have in this paper described the etiology, clinical profile and response of pain to therapy of patients with chronic pancreatitis seen at the Christian Medical College, Vellore.

Methods

Etiology assessment

History*:* The etiology of chronic pancreatitis was considered alcohol related if significant alcohol (more than 40gm per day) was consumed for a period of more than 5 years. Etiology was considered to be trauma if there was significant trauma to upper abdomen that produced severe abdominal pain suggestive of pancreatitis. None of the patients studied gave history of cassava consumption. *Biochemical*: Fasting serum calcium, lipid profile and antinuclear antibodies were measured. *Genetic studies*: Cationic trypsinogen gene mutations (R22H, N29I) and SPINK 1 gene mutation (N34S) were studied in 52 patients – 22 patients less than 20 years of age (early onset) and 30 patients more than 20 years of age (late onset).

Subjects: One hundred and seventy three patients diagnosed to have chronic pancreatitis between 2000 and 2004 were included in this retrospective analysis. The majority of patients (50 to 60%) were from Bengal and Bihar while the rest were from Tamil Nadu and Kerala. Diagnosis of chronic pancreatitis was made on the basis of a typical history, together with one of the following imaging studies showing evidence of chronic pancreatitis: pancreatic calcification on plain x-ray abdomen, ultrasound abdomen, CT abdomen and ERCP.

Results

Table 1 shows the etiology of chronic pancreatitis in patients studied. Fifty five patients (32%) had alcohol related pancreatitis. The majority of patients (55%) were diagnosed to have idiopathic chronic pancreatitis. Pancreas divisum was seen in 9%, hyperlipidemia in 2%, trauma abdomen in 1% and autoimmune pancreatitis in 1% of the patients studied. Table 1 of 2 shows the age of onset of pain. None of the patients showed cationic trypsinogen gene mutations (table 3). In early chronic pancreatitis, 54.5% showed heterozygous mutation and 13.6% shows homozygous mutation of SPINK 1 gene (N34S). In late chronic pancreatitis, 30% of patients showed heterozygous mutation of SPINK 1 gene (N34S). (The rest of the clinical profile of our subjects is described in a set of tables from 4 to 9.)

Table 1: Etiology of chronic pancreatitis (n = 173)

Alcohol	55 (32%)
Pancreas Divisum	15 (9%)
Hyperlipidemia	3 (2%)
Trauma – Abdomen	2 (1%)
Autoimmune	2 (1%)
Idiopathic	96 (55%)

Table 2: Age of onset among the subjects

	Early onset (< 20y) n = 22	**Late onset (> 20y) n = 30**
Mean age (y)	15 ± 3.5	34.2 ± 9
Mean age of onset of pain	12.7 ± 0.9	31.4 ± 1.9

Table 3: SPINK 1 gene mutations

SPINK 1 gene mutations (N34S) in early CP 12 / 22 (54.5%) heterozygous 3 / 22 (13.6%) homozygous
SPINK 1 gene mutations (N34S) in late CP 9 / 30 (30%) heterozygous

Note: Cationic Trypsinogen gene mutations (R122H; N29I) were not present in both early and late onset idiopathic chronic pancreatitis.

Table 4: Age and gender distribution of Patients with alcohol related and idiopathic chronic pancreatic

	Age (y)	Sex (M/F)
Alcohol	39.8 (28 – 61)	55 / 0
Idiopathic	35.7 (14 – 58)	63 / 33

Table 5: Symptom profile of Patients with alcohol related and idiopathic chronic pancreatic

	Alcohol (n = 55)	Idiopathic (n = 96)
Pain	55 (100%)	87 (91%)
Vomiting	33 (60%)	42 (44%)
Weight loss	25 (45%)	45 (47%)

Table 6: Complications in subjects with chronic pancreatitis

	Alcohol n = 55	Idiopathic n = 96
Pseudocyst	15 (27%)	5 (5%)
Pancreatic ascites	5 (9%)	3 (3%)
Jaundice	1 (2%)	3 (3%)
Diabetes Mellitus	16 (29%)	28 (29%)
Steatorrhoea	7 (7%)	12 (13%)
Carcinoma pancreas	5 (9%)	6 (6%)

The frequency of diabetes was similar in both alcohol related and idiopathic chronic pancreatitis. Frequency of steatorhoea was more in idiopathic chronic pancreatitis as compared to alcohol related pancreatitis (13% Vs 7%). Pseudocyst was the most common local complication. Duct disruptive complications like pseudocyst and pancreatic ascites were more common in alcohol related as compared

to idiopathic chronic pancreatitis (Pseudocyst: Alcohol related Vs Idiopathic chronic pancreatitis; 27% Vs 5%; Pancreatic ascites: Alcohol related Vs Idiopathic chronic pancreatitis; 9% Vs 3%). The frequency of carcinoma pancreas was similar in alcohol related and idiopathic chronic pancreatitis. Results of medical therapy, endotherapy and surgery are shown in Tables 7-9. *Medical therapy :* 85 of 173 patients were treated with pancreatic enzyme supplements for abdominal pain and followed for a minimum period of 6 months. Eighteen percent had complete relief of pain, 60% had partial relief and 22% did not respond to therapy. *Endotherapy :* 46 of 173 patients (37%) underwent endotherapy for relief of abdominal pain. Sixty seven percent had complete / partial response and 13% had no response. Twenty percent were lost to follow up. *Surgery* : 34 of 173 patients (20%) underwent surgery for abdominal pain. Twenty four of the operated patients were followed for 1 to 5 years. About 63% had complete relief of pain and 37% had partial response.

Table 7: Results of medical therapy

No response	19 / 85 (22%)
Partial response	51 / 85 (60%)
Complete response	15 / 85 (18%)

Note: 85 patients were followed up for a minimum of 6 months

Table 8: Results of endotherapy

Patients who underwent endotherapy	46 / 173 (27%)
Sphincterotomy + stent	30
Sphinc. /NPD/ESWL/Stone extraction	16
No response	6 / 46 (13%)
Partial / complete response	31 / 46 (67%)
Lost to follow up	9 / 46 (20%)

Table 9: Results of surgical therapy

Patients who underwent surgery	**34 / 173 (20%)**
Modified pancreatico-jejunostomy	24 / 34
Others	10 / 34
Patients followed up for 1 – 5 y (n=24)	
Partial response	9 / 24 (37%)
Complete response	15 / 24 (63%)

Conclusions

From the results of our study, we conclude that Idiopathic chronic pancreatitis is the most common form of chronic pancreatitis seen in Bengal and Tamil Nadu. Cationic trypsinogen gene mutations were not seen in early and late onset chronic pancreatitis. Heterozygous SPINK 1 gene mutation was present in 55% of early onset chronic pancreatitis and 30% of late onset chronic pancreatitis. Homozygous SPINK 1 mutation was present in 14% of early onset of chronic pancreatitis. Most patients presented in 2nd and 3rd decade of life. Duct disruptive complications were more often seen in alcohol related chronic pancreatitis as compared to idiopathic chronic pancreatitis. Diabetes mellitus was present in 29% and steatorrhoea in about 10% of patients. About 78% of patients treated with enzyme supplements had partial or complete response of abdominal pain. Surgery was better than endotherapy for pain relief in chronic pancreatitis.

Chapter 11

Tropical pancreatitis – changing trends

Vinayakumar KR, Biju Lal

Summary

The pattern of tropical pancreatitis as seen at our centre is changing. From our observations we conclude that tropical pancreatitis is now running a milder course with a late onset of symptoms and better longevity. We attribute the changes in the environmental factors to this better profile. These environmental factors include improvements in socio-economic status of the people of Kerala, better nutrition, replacement of cassava by other food items like rice, and better hygiene, less infections and more protein intake, despite of increasing alcohol intake.

Introduction

Tropical pancreatitis is a clinical entity accounting for majority of cases of chronic pancreatitis in South India. Originally described as "Pain in childhood, diabetes mellitus by puberty and death in the prime of life", this disease is also characterised by varying degrees of steatorrhoea, and calculi in pancreatic duct. Abdominal pain was the initial manifestation in majority of cases and the pain used to be very severe leading to narcotic addiction and suicide attempts. Diabetes mellitus was brittle, ranging from very high blood glucose levels to fatal hypoglycemia. These patients have a peculiar appearance characterised by wasting of muscles, protuberant abdomen, parotid swelling and cyanotic hue of lips. The main complications of the disease were uncontrolled diabetes mellitus, hypoglycemia, recurrent infections and liver disease. Also, there were local complications like pseudocyst formation, development of carcinoma pancreas, pancreatic ascites and obstructive jaundice.

Etiological factors thought to be important in the genesis of this disease include protein malnutrition, high carbohydrate intake in the form of cassava, toxins in food, especially cyanogenic glycosides of cassava, parasitic infections and probably genetic factors.

Over the last three decades there has been a considerable change in the natural history of tropical pancreatitis. The disease now affects an older population and has become less severe. In the majority of the patients abdominal pain is neither the first symptom nor a dominant

symptom. Diabetes mellitus is mild and is easier to control, but the microvascular complications have become prominent. Another important feature is the emergence of carcinoma pancreas as a leading complication and the most important cause of mortality.

This study was conducted at the Medical College, Kottayam from April 2000 to June 2001 and included 52 patients. Here we compare the findings in our patients with the data from two earlier studies from Kerala, by Geevarghese in 1968 and by Balakrishnan V in 1980.

Materials and methods

All patients admitted with a history suggestive of pancreatitis were evaluated. We included subjects with pancreatic calculi demonstrable by imaging studies, any stone size in non alcoholic and stone size > 7mm in alcoholics and excluded subjects with significant history of chronic alcohol use. All the patients who were included in the study were evaluated in detail. Detailed clinical history was taken with particular reference to the onset of illness, the first symptom, the character and severity of abdominal pain and the duration, control and complications of diabetes mellitus and history of steatorrhoea. Details regarding dietary habits, alcohol intake, smoking and malnutrition were obtained. Family history regarding similar illness and diabetes mellitus was also taken. Physical examination was performed with particular attention to nutritional status of the patient, signs of fat-soluble vitamin deficiency, signs of protein malnutrition and features of local complications. Cardiovascular system evaluation included physical examination, chest X ray, ECG, 2D Echo and TMT when needed. Nephrological evaluation included tests for microalbuminuria and renal functions. Neurological evaluation was done for evidence of diabetic/ nutritional peripheral neuropathy, tropical spastic paraplegia and tropical ataxic neuropathy. An ophthalmologist performed ophthalmologic evaluation for evidence of retinopathy. The patients also underwent imaging studies ranging from plain X ray of abdomen to ERCP. USG abdomen was performed in all the patients. Other investigations included fasting and postprandial blood sugar levels, liver function tests and analysis of ascitic fluid/pleural fluid and FNAC of suspicious mass lesions and endoscopic studies.

The results

Total 52 patients were studied: 34 males and 18 females. The mean age of patients at the time of inclusion in the study was 42.9years. Tables 1 and 2 show the clinical profile of the patients.

Table 1: Initial symptoms

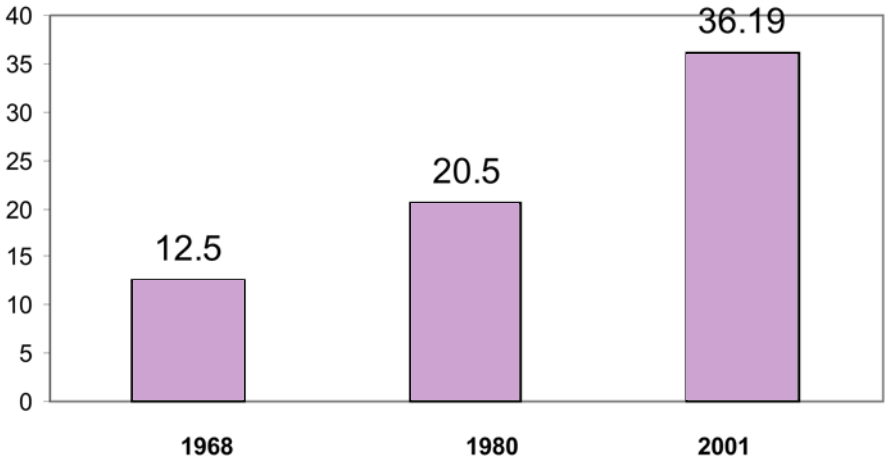
	Males	Females	Total	%
Diabetes Mellitus	19	13	32	61.5
Abdominal pain	13	3	16	30.8
Others	2	2	4	7.7

Diabetes mellitus is the leading presenting symptom accounting for 61.5% of the patients. It is especially so in females, where diabetes is the first symptom in 72.2%. Abdominal pain is the presenting symptom in only 30.8% of cases. This is in contrast with previous studies where abdominal pain was the initial symptom in 83.3% patients.

Table 2: Age of onset of first symptom

Age	Male	Female	Total
< 10	0	0	0
10 – 15	2	0	2
16 – 20	1	3	4
21 – 25	5	2	7
26 – 30	6	3	9
31 – 35	4	2	6
36 – 40	6	0	6
41 – 45	2	5	7
46 – 50	2	0	2
51 – 55	4	1	5
> 55	2	2	4

Fig. 1: Mean age of 1st symptom - a comparison with earlier studies



As shown in table 1, compared with previous studies there is a remarkable shift in the initial presentation of the illness. The mean age of onset of the disease has shifted by more than two decades.

Table 3: Age of onset of diabetes mellitus

Age	Male	Female	Total	%
< 10	0	0	0	0
10 – 15	0	0	0	0
16 – 20	1	2	3	7.7
21 – 25	3	2	5	12.8
26 – 30	3	2	5	12.8
31 – 35	3	4	7	17.9
36 – 40	7	0	7	17.9
41 – 45	1	4	5	12.8
46 – 50	3	0	3	7.7
51 – 55	2	1	3	7.7
> 55	0	1	1	2.6

Fig. 2: Age of onset of diabetes mellitus – a comparison with 1968 figures

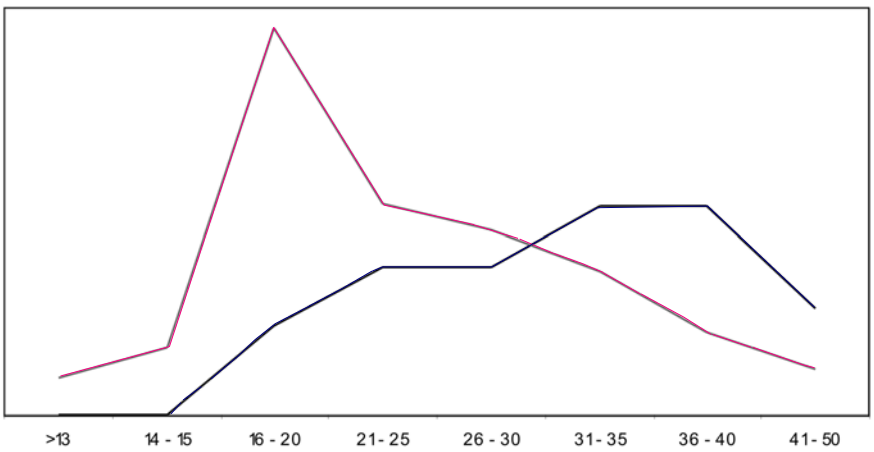
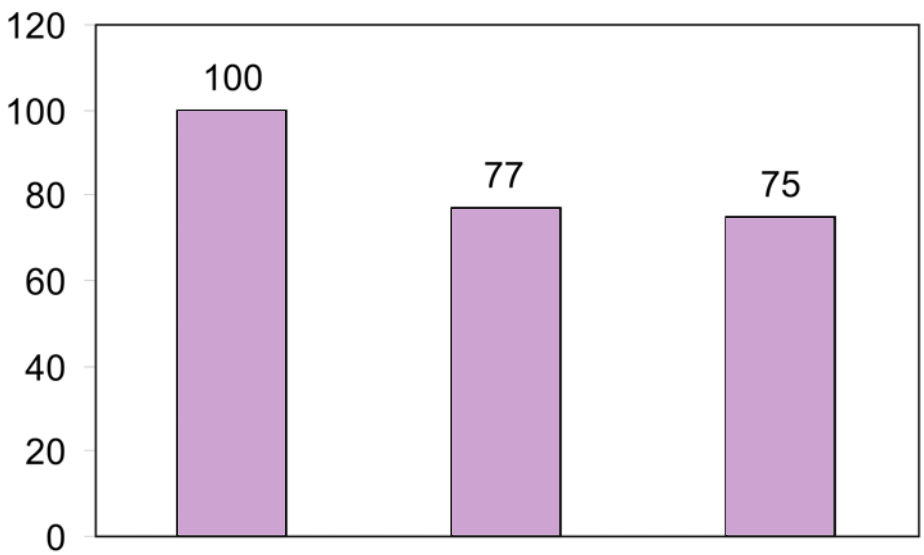


Fig. 3: Incidence of diabetes mellitus – a comparison with earlier studies



Diabetes control

Mean FBS of the patients were 172.6mg%, and the PPBS of the patients were 243.7 mg%. 19 patients were on oral hypoglycemics only. Their mean FBS was 174.1mg% and PPBS was 225.8mg%. About 17 patients were on insulin, their mean FBS was 189.5mg% and PPBS was 278.2 mg%.

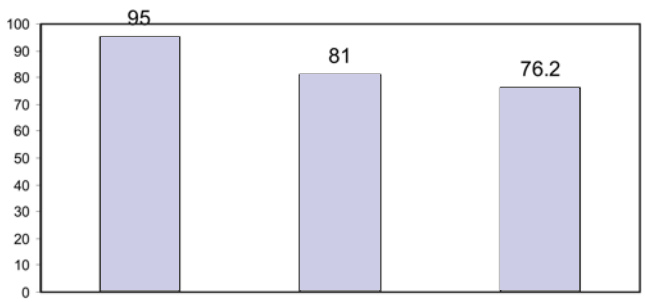
Microvascular complications

Microvascular complications were present in 16 patients – peripheral neuropathy in 16 patients, retinopathy in 11 patients and nephropathy in 6 patients. Their mean duration of diabetes mellitus was 11.9 years, compared to those without microvascular complications, whose mean duration of diabetes was only 4.09 years, indicating that duration of diabetes mellitus determines the microvascular complications. (Microvascular complications usually occur in the second decade of chronic hyperglycemia – Harrison). This shows that microvascular complication depends on duration of diabetes alone and pancreatitis as such has no role in the genesis of microvascular complications.

Abdominal pain

Abdominal pain was the first symptom in 28.8% of patients only. But eventually 76.9% of patients developed abdominal pain. Diabetes Mellitus precedes abdominal pain in a significant number of cases. In previous studies it was very rare for diabetes mellitus to precede abdominal pain.

Fig. 4: Incidence of abdominal pain – a comparison with earlier studies



Carcinoma pancreas

Totally, there were 8 cases (15.4%) – 3 females and 5 males. Mean age 45 years. In 4 of these patients carcinoma pancreas was the presenting symptom In 3 diabetic patients, the beginning of abdominal pain was the symptom of carcinoma pancreas. All these 3 patients were diagnosed to have tropical pancreatitis, at the time of presentation as carcinoma pancreas.

Fig. 5: Carcinoma pancreas – a comparison with earlier studies

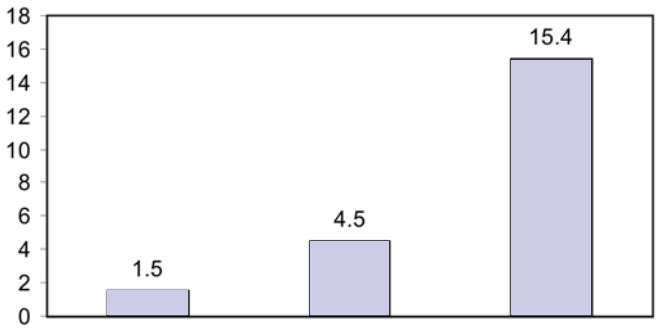


Fig. 6: Need for surgery – a comparison with earlier studies

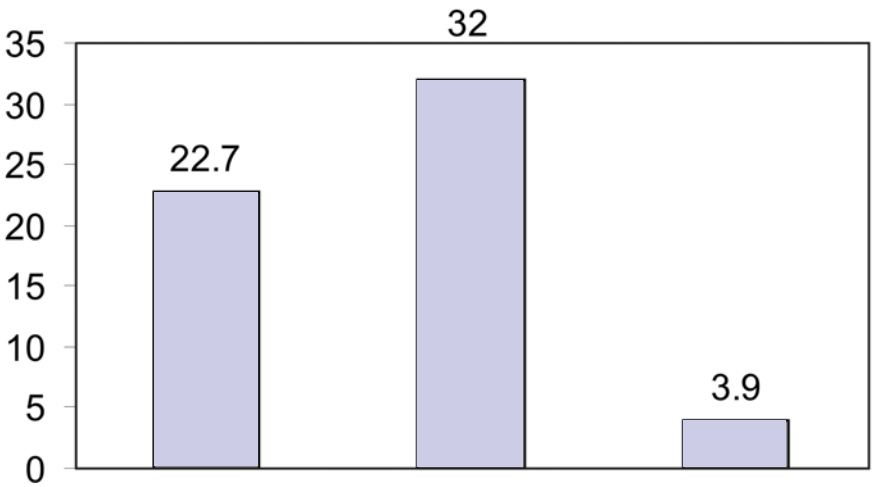


Table 4: Mortality in FCPD - a comparison

Causes of death
Carcinoma pancreas 66.66%
Carcinoma stomach 16.7%
Diabetic nephropathy 16.7%
Cause of death comparison
1968 – cirrhosis liver and hypoglycemia
1980 – diabetic nephropathy
2001 – carcinoma pancreas

Discussion

Our observations are that the onset of tropical pancreatitis has shifted by two decades. Tropical pancreatitis now constitutes a spectrum of disease ranging from the classical presentation (of pain in childhood, diabetes in puberty) to totally asymptomatic patients presenting as carcinoma pancreas, but the classical presentation is rare. Abdominal pain is neither the first symptom nor the dominant symptom; abdominal pain has decreased in severity and is easier to control. Microvascular complications of diabetes are common and are related to the duration of diabetes. Carcinoma pancreas can be the presenting symptom of tropical pancreatitis. Carcinoma pancreas is the leading cause of death in these patients. Alcohol has no etiological relation with tropical pancreatitis in our experience.

From these observations we conclude that overall, tropical pancreatitis is now running a milder course with a late onset of symptoms and better longevity. We attribute the changes in the environmental factors to this better profile. These environmental factors include improvement in socio-economic status of the people of Kerala, better nutrition, replacement of cassava with other food items like rice and better hygiene, less infections and more protein intake, in spite of increasing alcohol intake.

Table 5: Juxtaposing the changes in cassava production with the rising per-capita income

Cassava production		
1971	–	293020 hct. 4.61 m.tonne
1984	-	232753 hct. 3.95 m.tonne
1999	-	109257 hct. 1.97 m.tonne
Percapita Income		
1970	-	Rs. 594/-
1980	-	Rs. 1508/-
1990	-	Rs. 4200/-
1995	-	Rs. 11190/-
2000	-	Rs, 19465/-

Chapter 12

Exocrine pancreatic function in fibrocalculous pancreatic diabetes

Mathew Philip, Balakrishnan V

Summary

In fibrocalculous pancreatic diabetes (FCPD), manifestations of pancreatic exocrine deficiency are variable and clinical presentation with steatorrhoea is uncommon. However objective tests of pancreatic exocrine functions are generally abnormal in FCPD, which represents a late stage of the disease. Though considered to be the gold standard, direct pancreatic function tests such as secretin-pancreozymin (CCK) test and Lundh meal test are time consuming, invasive, expensive and hence beyond the reach of non-specialized centers. Stool fat estimation is cumbersome and difficult to set up and perform routinely. Most of the centers now perform simple tests such as faecal chymotrypsin. Fecal elastase is being more commonly used in many centers. Though this is very specific, it is sensitive only in advanced stages of the disease. With the wide availability of imaging of the pancreas by ultrasound, computerized tomography, endoscopic retrograde pancreatography and magnetic resonance pancreatography, early and noncalcific stages of the disease can be diagnosed with reasonable certainty. In these situations exocrine pancreatic function tests are not an absolute necessity for the diagnosis of chronic pancreatitis and are mainly used for assessing the extent of exocrine pancreatic dysfunction. The need of the hour is for more sensitive, simple and less expensive exocrine pancreatic function tests, which could also be used for screening purposes.

Introduction

Fibrocalculous pancreatic diabetes (FCPD) is characterized by diabetes presenting at a young age secondary to chronic calcific nonalcoholic pancreatitis. This is more common in tropics and is synonymous with tropical calcific pancreatitis (TCP). Exocrine pancreatic deficiency is common. Clinical manifestation of steatorrhoea may be seldom noticed (<20%), though objective tests for exocrine function often show abnormal results. This is thought to be due to the low fat intake by the patients.[1] A variety of tests are available to assess exocrine function in chronic pancreatitis but their published use in tropical calcific pancreatitis is limited. The role of exocrine pancreatic function tests (PFT) in diagnosis of chronic pancreatitis has diminished considerably due to advances in imagining modalities such as ultrasound scan, computerized

tomography, and endoscopic retrograde pancreatography and magnetic resonance pancreatography. Pancreatic function tests are very valuable in cases of chronic pancreatitis particularly when imaging modalities are inconclusive; unfortunately only invasive tests are sensitive in mild cases. They are also valuable to determine if pancreatic insufficiency is contributing to malabsorption, to determine the adequacy of pancreatic enzyme replacement therapy and to assess the extent of insufficiency before undertaking pancreatic resection as a part of surgical management.

Pancreatic exocrine function tests may be direct tests or indirect tests. In the direct tests the parameters of pancreatic secretion are measured in duodenal or pure pancreatic juice after stimulation of the pancreas. The secretin- pancreozymin (CCK) test is considered as the gold standard with false positive of 8% and false negative of 6%. Lundh meal test is simple and physiological. A variety of indirect tests are available which include stool tests like faecal fat estimation, faecal chymotrypsin, faecal elastase, faecal immunoreactive lipase, serum tests of pancreatic enzymes particularly is amylase and immunoreactive trypsin; NBT -P ABA (N-Benzoyl -2- Tyrosil- P- amino benzoic acid) and pancreolauryl tests. Other tests include breath analysis test, dual labeled Schilling test and plasma amino acids estimation after stimulation with secretin and pancreozymin. The results of indirect PFT depend on the severity of exocrine pancreatic insufficiency. In cases of mild exocrine pancreatic insufficiency all indirect PFT may yield falsely normal results.

The data on exocrine pancreatic functions in TCP is limited mainly because the previously available tests of PFT were laborious and expensive. Since their introduction simple and less expensive tubeless tests of pancreatic function are more widely used.

Direct tests

Lundh meal test is simple and valuable in assessing exocrine deficiency in tropical pancreatitis. In a series reported by Punnose et al the mean tryptic activity was less than 2 iu/ml in 93% of the calcific group and 27% in the non-calcific group with a cut off level of 12.4 iu/ml in the controls. Calcification seemed to correlate with a gross reduction of tryptic

activity though this did not strictly correlate with the degree of steatorrhoea. Ninety percent of TCP patients had subnormal duodenal tryptic activity.[2] Reduction of tryptic activity in one hundred percent of patients with chronic pancreatitis was reported from Chandigarh. [3]

Secretin-pancreozymin (CCK) test, using a special double lumen tube with a pyloric balloon, was done by Balakrishnan and Sarles in TCP patients and south Indian controls (adults and children). The duodenal aspirate was analyzed for volume, pH, bicarbonate, calcium, lipase, phospholipase, trypsin, chymotrypsin and lactoferrin. They compared their findings with those from alcoholic chronic pancreatitis patients from Marseille, France and French controls. The analysis showed high calcium content in Indian patients and controls, with marked reduction of phospholipase values in Indian patients. The volume and bicarbonate levels were markedly reduced while the lactoferrin values in the duodenal aspirate were elevated in Indian patients. [1] In one earlier report by Chirayath using the secretin- pancreozymin (CCK) stimulation test the volume, HC03, amylase and lipase of duodenal contents were studied; volume was reduced in 40%, HC03 reduced in 50% of cases, amylase in 10% and lipase in 80% of cases. [4] Secretin-pancreozymin (CCK) test done by Tripathy et al in a small group of FCPD patients showed that pancreatic enzyme output was grossly diminished, trypsin more affected than amylase. [5] In another study by Sarles and Augustine pure non-activated pancreatic juice was collected at endoscopy in 10 Indian TCP patients, 12 normal South Indian and 23 normal French controls. The pancreatic juice of TCP was characterized by decreased volume, normal bicarbonate, increased protein and calcium concentration with normal citrate concentration. During cerulein stimulation there was no significant difference in protein concentration between TCP patients and Indian controls. The changes were very similar to those observed in French patients with chronic alcoholic pancreatitis.[6]

Indirect tests

Serum levels of enzymes

Estimation of serum level of amylase and lipase are not found to be useful in TCP and even in acute exacerbation the values are usually not elevated. [7] However lipase levels were reported to be significantly lower

than controls in some studies. [8] Evocative serum enzyme studies (after stimulation with secretin- pancreozymin) did not show any rise in amylase or lipase levels. [4] Serum immunoreactive trypsin (IR T) levels were assayed for exocrine pancreatic function in FCPD by Yajnik et al and 93 percent of patients had low IRT levels. [9] IRT and C peptide levels were clinically correlated. [10] In another study the same group observed that, in TCP subjects with normal glucose tolerance and impaired glucose tolerance, the IRT levels were subnormal in a few cases while in FCPD these were severely reduced in more than two third of the patients. Elevated levels of IRT seen in early stages of the disease may suggest active pancreatitis. However a third of their IDDM and some of their NIDDM patients also showed subnormal IRT levels. They suggested IRT level as a simple marker for exocrine pancreatic function. Serum pancreatic iso-amylase [PIA] levels in FCPD patients were significantly lower than controls. [11] Although PIA is highly specific, it is not sensitive enough to be used as a screening test for exocrine pancreatic deficiency; however it could be used to determine the etiology of steatorrhea.[12]

Is there an entity called "Subclinical pancreatopathy of tropics"? In their landmark paper, Balakrishnan and Sarles made the interesting observation that even many of their south Indian controls had subnormal secretion of pancreatic enzymes and very high calcium levels in their pancreatic juice, compared to French controls, and put forth the interesting concept of an entity of "Subclinical Pancreatopathy of the Tropics". [1] They also found a high carbohydrate, low potein and very low fat intake in the diet of their south Indian patients and controls, and proposed the hypothesis that the imbalanced dietary intake might be a possible cause for the pancreatic functional alterations in their "normal" controls.[1] Subsequently, in another study, subnormal values of IR T have been shown in controls from tropics.[17]

Faecal tests

Stool fat estimation: In the past, 24 hrs stool fat estimation by Van de Kamer method was the most commonly done test to assess exocrine pancreatic function but seldom used now. Only a minority of TCP patients complain of clinical steatorrhoea, as their fat intake is low. Analysis of

the diet of TCP patients studied by Balakrishnan et al showed mean daily fat consumption of 27g only .On a high fat diet (100 g butter) steatorrhoea was noted in 76% (24hr stool fat averaged I8.43gm). [7]

Faecal chymotrypsin (FCT): Faecal chymotrypsin in FCPD studied by Mohan et al showed abnormal values in 87.5% of patients. [8] FCT is considered abnormal if the test value is less than 6 ulgm. FCT estimation is simple and can be done in small institutions with minimal equipment The disadvantage is that as with other tubeless pancreatic function tests FCT is not sensitive in early disease. In FCPD, which represents advanced disease, FCT values are almost invariably abnormal. Since FCT is less expensive and easier to perform, this test is the preferred exocrine pancreatic function test in FCPD. There are several reports using faecal chymotrypsin as a screening test for evaluating exocrine pancreatic function in TCP patients. [8,11,19] FCT was screened in three groups of diabetic patients with FCPD and type 1 and type 2 diabetes and found that exocrine pancreatic insufficiency as shown by low faecal chymotrypsin levels (defined as, 5.8 units/g of faecal mass) was present in 87.5% of patients with FCPD, 23.5% with type 1 diabetes, and 4.5% with type 2 diabetes.[8]FCT was studied in three groups of TCP patients having variable glycemic status (normal glucose tolerance, Impaired GTT, and DM). Mean FCT levels in all 3 subgroups were very low, 87-96% reduction in exocrine pancreatic dysfunction. [20]

Low sensitivity is the only drawback with faecal chymotrypsin, as it may not detect many mild cases of chronic pancreatitis, although its specificity is quite high. In a study faecal chymotrypsin was compared with another tubeless test, N-benzoyl L–tyrosyl–para-aminobenzoic acid (BT-PABA) test. [18] Although the faecal chymotrypsin test has a slightly lower sensitivity, it is simpler and considerably cheaper than the PABA test. However the BT-PABA/p-amino salicylic acid is a more efficient test to diagnose TCP as it has a very high sensitivity and specificity. [15] Among malnutrition related diabetes of north Indian patients FCT levels were significantly lower in subjects with FCPD (median 0.4 U/g, range 0-8.9 U/g), in comparison with those with PDPD (4.7 U/g, 0.6-40.5 U/g; $P < 0.001$). Of the FCPD patients, 13 of 20 (65%) had severe exocrine pancreatic deficiency (FCT < 1 U/g) vs. 3 of 19 (15.8%) PDPD subjects ($P < 0.01$). [21] However another study from Delhi on a smaller number of

patients found the exocrine function using stool fat estimation were comparable among these two groups. [22] Newer faecal tests such as immunoreactive lipase and faecal elastase are promising simpler tests but have low sensitivity in mild disease and utility in FCPD has to be further evaluated.[13,14]

Miscellaneous tests

NBT- PABA / PAS test showed sensitivity of 75% and specificity of 81 % in tropical pancreatitis. PABA / PAS excretion index (PEI) showed a sensitivity of 75% and specificity of 92%, using a cut off value of 0.75. [15] The usefulness of this test as a screening test in field surveys of tropical pancreatitis has to be substantiated by further studies. In a comparative study of NBT PABA test and FCT, one hundred percent of FCPD patients had abnormal NBT PABA test while 92.3% had abnormal FCT.[16]

Yajnik et al in a comparative study of IRT, FCT, and PIA suggested a possible sequence of events in TCP. FCT levels come down progressively in TCP while IRT levels may be elevated or normal in the early stages due to disease activity. In advanced stages of TCP both tests are severely affected. Trypsin secretion seems to be affected earlier than amylase as evidenced by preservation of PIA levels till late stages of the disease. Similarly FCT level was reduced even while serum amylase and lipase levels were normal.[11]

References

1. Balakrishnan. V, Sauniere. IF, Hariharan M, Sarles H. Diet pancreatic function chronic pancreatitis of south India and France. Pancreas 1988;3:30-35
2. John Punnose, BalakrishnanV, Bhadran A, Krishnadas KV. Exocrine pancreatic function in chronic pancreatitis with and without calcification. Indian / Gastroenterol 1987; 6:85- 86
3. ChawlaLS,SehgaIAK, VermaRS,BalakrishnanV, Chuttani.PN. Lundh test in the diagnosis of exocrine pancreatic insufficiency. Indian / Med Res 1973;61 :700-703
4. Henry Chirayath.Exocrine pancreas in pancreatic diabetes. In NarayanaPaiK, SomanCR,RoyV arghese,eds:Pancreaticdiabetes. Geoprinters, Trivandrurn,India: 1970; 16- 27.

5. TripathyBB.Diabetes with exocrine pancreatic disease. In Bajaj IS ed, Diabetes in developing countries.Interprint,New Delhi. 1984; 135-142.

6. Sarles H, AugustineP ,LaugierR,Mathew S,Dupuy P .Pancreatic lesions and modification of pancreatic juice in tropical chronic pancreatitis(tropical calcific pancreatitis).Dig Dis Sci.1994;39:.1337-44.

7. Balakrishnan V. Tropical palicreatitis(pancreatitis tropicale),in B.ernades P ,HugierM ;ed Maladies du pancreas exocrine,Doin,Paris.1987;207-227

8. Mohan V ,SnehalethaC,AhmedMR,MadanagopalanN etal. Exocrine pancreatic function in tropical fibrocalculous pancreatic diabetes.Diabetic care 1989;12: 145-147.

9. YajnikCS,KatrakA,KanitkarSV,NaikSS etal.Serum immunoreactive trypsin in tropical pancreatic diabetes syndrome. Ann clin B iochem.1989 ;26: 69- 73.

10. YajnikCS,ShelgikarKM,SahasrabudheRA etal.Spectrum of pancreatic exocrine and endocrine(beta cell) function in tropical calcific pancreatitis.Diabetologia 1990;33:417- 421.

11. YajnikCS,SahasrabudheRA,NaikSS,KatrakAetal.Exocrine pancreatic function (serum immuno reactive trypsin,faecal chymotrypsin and pancreatic isoamylase) in Indian diabetics. Pancreas 1990;5 :631-3 8

12. LankischPG,KoopH,OttoI.Estimation of serum pancreatic isoamylase:its role in the diagnosis of exocrine pancreatic insufficiency..Am J Gastroenterol.1986;81:365-368 13.MuenchR,AmmanR.Faecal immunoreactive lipase:a new tubeless pancreatic function test.Scand J Gastroenterol.1992;27:289-94.

13. Dominguez- MunozJE,HieronymusC, Sauerbruch T ,MalfertheinerP .F aecal elastase test: evaluation of a new noninvasive pancreatic function test.Am J,. Gastroenterology. 1995;90:1834-7 .

14. Gagee P,Pemberton P,Lobley R,Chaloner C etal.The BT-PABA/PAS test in tropical diabetes.Clinica Chemica Acta 1992;212:103-111

15. MohanV.Comparison of exocrine pancreatic function by two tubeless tests in fibrocalculous pancreatic diabetes (FCPD) and insulin dependant diabetes mellites(IDDM).Int J Diab Dev countries.1996:16:61-64

16. Yajnik CS .Diabetes secondary to tropical calcific pancreatitis .Balliere's clinical endocrinology and metabolism 1992;6:777-796

17. Mohan V. Comparison of exocrine pancreatic function by two tubeless tests in fibrocalculous pancreatic diabetes (FCPD) and insulin dependent diabetes mellitus (IDDM). International Journal of Diabetes in Developing Countries 1996;16:61–4.

18. Wiyono P. Exocrine and endocrine pancreatic function in malnutrition related diabetes mellitus (MRDM) in Yogjakarta. Kobe J Med Sci 1988;34:215–26.

19. Sidhu SS, Shah P, Prasanna BM, Srikanta SS, Tandon RK. Chronic calcific pancreatitis of the tropics (CCPT): spectrum and correlates of exocrine and endocrine pancreatic dysfunction Diabetes Res Clin Pract. 1995 Feb;27(2):127-32.

20. Bhatia E, Baijal SS, Kumar KR, Choudhuri G Exocrine pancreatic and beta-cell function in malnutrition-related diabetes among north Indians..Diabetes Care. 1995 Aug;18(8):1174-8.

21. Saraya A, Acharya SK, Vashisht S, Tandon RK. A pancreaticographic study of malnutrition-related diabetes mellitus .Trop Gastroenterol. 2003 Jul-Sep;24(3):120-3.

Chapter 13

Chronic calcific pancreatitis of the tropics with carcinoma

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Summary

Background*: Carcinoma developing in chronic calcific pancreatitis of the tropics (CCPT) is a well known complication. Early diagnosis is difficult and the overall mortality rate is high. Clinically and pathologically, this malignancy behaves in a different manner compared to denovo pancreatic ductal adenocarcinoma. This paper analyses and compares pancreatic carcinoma occurring along with CCPT and denovo carcinoma.*

Methods: *One hundred and forty one cases of carcinoma pancreas seen in the Departments of Medical and Surgical gastroenterology, Medical College, Trivandrum, during a 4-year period from January 1993 to December 1996 were retrospectively and prospectively studied. The data were analyzed as 2 groups: Group A – CCPT with malignancy, Group B – patients with denovo pancreatic ducal adenocarcinoma with no CCPT.*

Results: *There were 23 cases of malignancy in CCPT (Group A) and 118 patients belonged to Group B. Group A patients had a significantly lower age, median age was 38 years (28-61 years) and duration of symptoms ranging from 3 months to 15 years.*

Intractable pain, significant loss of weight and worsening of diabetes were the commonest presenting symptoms in cancers with CCPT, noted in 60% of cases. Jaundice, pruritus and loss of weight were the commonest presentation in denovo cancers. The distribution of tumours was similar in Groups A and B with maximum involvement of the pancreatic head.

Hepatic metastases were less common for malignancies developing in CCPT, Group A. In Group A local invasiveness of the tumour was high and overall resectability of the tumour was poor. ***Conclusion:*** *Carcinoma occurs in approximately 25% of cases of CCPT. There is a predilection for involvement of head of pancreas. However, involvement of body and tail of pancreas is higher than denovo pancreatic cancer. Both local infiltration and peritoneal dissemination are higher in CCPT with carcinoma, but liver metastasis is rare.*

Introduction

The premalignant nature of CCPT has been established by many prospective and retrospective studies[1-6]. Development of malignancy, at some stage, is seen in less than 1/3rd cases of CCPT in the state of Kerala where CCPT occurs in endemic proportions[7,8]. Earlier studies from our department had shown that carcinoma arising in patients who have CCPT behave in a different manner clinically and pathologically, compared to denovo pancreatic cancer[1,3,4]. This retrospective and prospective study tries to analyze and compare carcinoma occurring in CCPT to denovo pancreatic cancer.

Methods

This retrospective and prospective study is based on 141 cases of histologically proven pancreatic carcinoma, 23 of whom had CCPT, that were operated in the Department of Surgical Gastroenterology, Medical College Hospital, Trivandrum, during a period of 4 years from 1993-1996. Standard clinical and radiological criteria were used to diagnose CCPT, which included history of abdominal pain, sonological evidence of dilated pancreatic duct with calculi, ERCP findings and CT scan.

The diagnosis of pancreatic carcinoma was by histopathologic examination of per-operative tru-cut biopsy or resected specimen of the pancreas. For comparison and analysis of data, patients were divided into 2 groups: Group A included CCPT presenting as malignancy and Group B consisted of patients with denovo pancreatic ductal adenocarcinoma and no CCPT. Clinical presentation, morphology and operative findings of these tumours were analyzed.

A total number of 98 cases of CCPT were seen and evaluated in gastroenterology clinic during the study period. Forty three cases underwent various surgical procedures for CCPT and 23 cases (24%) were done for malignancy.Age distribution showed a significant difference of about a decade between each groups, the lowest being in Group A with a median age of 38 years in comparison with Group B (the median age was 54 years). Male preponderence was similar in both groups. Endocrine insufficiency in the form of diabetes mellitus was found in 66% of patients in Group A, but only 19.4% of patients in Group B (Table 1).

Table 1: General features

	Group A	Group B
Total number of cases	23	118
Sex ratio (M:F)	1.6:1	2.19:1
Median age	38 years	54 years
Jaundice and pruritus	70%	86%
Diabetes mellitus	66%	19.4%

Symptoms were analyzed by allotting a scoring system (Table 2 and 3). A score of 5 was observed in 29% of cases belonging to Group A while none of the Group B cases could satisfy the maximum score of 5. The tetrad of jaundice, worsening of diabetes, change in character of pain and significant loss of weight were observed in 60% of cases of Group A. Head of pancreas was the commonest site to be involved in both groups, but there was relatively higher predlection for the body and tail in Group A, when compared with Group B. Distribution of calculi however, was more uniform throughout the gland and no significant relation was found between the location of tumour and calculi.

Table 2: Symptom score

Sl. No.	Symptoms	Score
1	Worsening of diabetes	1
2	Change in character of pain	1
3	Loss of weight	1
4	Jaundice	1
5	Pruritus	1

Table 3: Symptom score in relation to groups

Score	Group A	Group B
0-2	16%	37%
2-4	55%	63%
5	29%	0

Table 4: Location of tumour (Predominant region of cancer involvement)

Location of tumour	Group A	Group B
Head of pancreas	15 (65%)*	106 (90%)
Body of pancreas	4 (17%)**	10 (8.5%)
Tail of pancreas	1 (5%)	2 (1.5%)

* Two cases of CCPT with suspicion of carcinoma of head of pancreas were excluded as peroperatively no tumour was found; however, pathological examination of tissue specimens were positive.

** One case of CCPT with suspected carcinoma of body of pancreas was excluded as preoperatively it was diagnosed as intraductal papillary adenocarcinoma.

Local infiltration to adjacent organs and major vessels were significantly high in Group A. Peritoneal dissemination was higher in Group A as well. Lymph node (LN) metastasis was also slightly higher in Group A (Table 5). Liver metastasis at presentation was significantly more common in Group B compared to Group A. Majority of patients underwent only palliative procedures because of either locally advanced or metastatic disease in Group A.

Table 5: Operative findings

	Group A	Group B
Local infiltration	9 (39%)	24 (20%)
LN metastasis	4 (17%)	12 (10.2%)
Peritoneal metastasis	7 (30.4%)	10 (8.5%)
Liver metastasis	1 (4.3%)	22 (18.6%)

Discussion

Patients with CCPT present with abdominal pain, weight loss, pancreatic calcifications, and glucose intolerance or diabetes mellitus[7]. Kerala, the southwestern state of India has found to be one of the 'hot spots' with

high incidence of CCPT. The etiology of CCPT is largely unknown, and nutritional and environmental factors have been propagated as major causative factors in the etiopathogenesis. Postulated etiologies include a protein-calorie malnourished state, a variety of exogenous food toxins, pancreatic duct anomalies, and a possible genetic predisposition[7]. Chronic cyanide exposure from the diet may contribute to this disease. The cyanogenic glycosides linamarin and lotaustralin are contained in cassava. Cassava, a mainstay of many tropical and subtropical diets, especially in India, reacts with gastric hydrochloric acid, liberating hydrocyanic acid, which is toxic to cells[10,12]. Duration of exposure to inflammation seems to be the major factor involved in the transition from benign to malignant condition.

CCPT is identified as a premalignant condition and several studies have reported this fact earlier. In our series, CCPT co-existing with pancreatic cancer was 24% of the cases seen in the clinics. Malignancy developed at the prime of their life (median 38 years) in these patients (Group A). It is more than a decade earlier than the development of denovo cancers. An earlier study from this institution had reported pancreatic carcinoma developing in 22 of 240 patients with tropical pancreatitis on a 7-year follow up[8,9]. Clearly, there is an increased incidence of diabetes mellitus in cases with carcinoma in CCPT. Chari et al. followed 155 patients with TP from Madras, India, for an average of 4.5 years. They found that 25% of the deaths recorded in the group were from carcinoma of the pancreas. The average age for onset of pancreatic cancer was 45 years[5].

Change in character of pain, development of jaundice, recent worsening of diabetes and significant weight loss are considered predictors of malignancy in CCPT patients[3]. Jaundice, intractable pain, recent worsening of diabetes and marked weight loss were found in 60% of patients with CCPT presenting with carcinoma.

The distribution of tumours in the pancreatic gland in Group A was similar to that of Group B with a greater predilection for the head, unlike previous studies showing a high incidence of cancer of body and tail of pancreas[11]. There was a relatively higher involvement of the body than in denovo cancer of pancreas.

Though local aggressiveness of the tumour was found to be more when CCPT coexisted, visceral dissemination was uncommon. Peritoneal dissemination and lymphnode metastasis were found to be higher in CCPT with cancer. The local aggressiveness could be due to the biological features of malignant cell in CCPT and paucity of early visceral metastasis due to excessive fibrosis of the pancreas promoting an early peritoneal dissemination rather than a haematogenous spread. However, early diagnosis of carcinoma in CCPT is a vexing problem to the gastroenterologist because of the inability to localize the tumour precisely in a diffusely fibrotic gland with chronic pancreatitis.

References

1. Anandakumar M, Meenu H, Chellam VG, Prakash K. Is cancer complicating tropical pancreatitis (CCPT) different from pancreatic ductal adenocarcinoma (PDA)?. Proceedings of the 2nd International workshop on Mechanistic analysis and chemoprevention of pancreatic carcinogenesis, Nara, Japan, Nov 28-29; 1997.
2. Lowenfels AB, Maissoneve P, Pitchumoni CS et al. Pancreatitis and risk of pancreatic cancer. New Eng J Med. 1993; 328: 1433-7.
3. Hariharan M, Anandakumar M, Chellam VG et al. Association of pancreatic ductal adenocarcinomas with chronic calcifying pancreatitis of the tropics. Recent advances in Gastroenterological cancinogenesis II Hiroshima, Japan: 1996.
4. Augustine P, Ramesh H. Is tropical pancreatitis premalignant? Am. J Gastroenterol 1992; 87: 1005-8.
5. Chari ST, Mohan V, Pitchumoni CS et al. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. Pancreas 1994; 2: 62.
6. Chari S, Mohan V, Snehalatha C et al. Pancreatic carcinoma complicating tropical chronic pancreatitis – a follow up study. Gastroenterology 1992; 102: 260.
7. Geevarghese PJ. Calcific pancreatitis: causes and mechanisms in the tropics compared with those in the subtropics. Trivandrum: St. Joseph's Press, 1986: 67-75.
8. Narendranathan M, Shenoy KT, Hariharan M. Tropical pancreatitis – sequelae and complications: A prospective study. Proceedings of the Annual conference of the Indian Society of Pancreatology, Trivandrum Medical College, 1986; 16.

9. Narendranathan M. Chronic calcifying pancreatitis of the tropics. Trop. Gastroenterol. 1981; 2: 40.

10. Petersen, John. Tropical pancreatitis (liver, pancreas and biliary tract: clinical reviews: Pancreatic and biliary disease). Journal of Clinical Gastroenterology. 2002; 35(1): 61-66.

11. Thomas PG, Augustine P, Ramesh H, et al. Observations and surgical management of tropical pancreatitis in Kerala and Southern India. World J Surg 1990; 14: 32-42.

12. M Mori, Hariharan M, Anandakumar M, Chellam VG et al. A case control study on risk factors for pancreatic diseases in Kerala, India. Hepato-Gastroenterology 1999; 46: 25-30.

Chapter 14

Fibrocalculous pancreatic diabetes

Mohan V

Summary

This article is a state-of-the-art update on fibrocalculous pancreatic diabetes (FCPD). In addition to our studies on the etiopathogenesis and clinical profile of the illness, we also present the results of our work on the natural history as well as the long-term survival analyses of subjects with FCPD. The management of diabetes in FCPD is the same as for the other types of diabetes except that a more liberal calorie and protein intake may be advised because of the associated undernutrition. Oral hypoglycemic agents may be useful in cases with mild diabetes and relatively early in the course of the disease. However, the majority of patients eventually need insulin for control of diabetes and to improve their general health and sense of well-being.

Definition and terminology

Fibrocalculous Pancreatic Diabetes (FCPD) can be defined as a form of diabetes secondary to non-alcoholic chronic pancreatitis of uncertain etiology predominantly seen in tropical developing countries. Several terms had been earlier proposed for this syndrome including tropical calcific pancreatitis, tropical chronic pancreatitis, tropical pancreatic diabetes, nutritional pancreatitis, endemic pancreatic syndrome, etc. As the term Fibrocalculous Pancreatic Diabetes was introduced by the World Health Organization Report (1) this is the preferred term used by diabetologists while the term Tropical Calcific Pancreatitis (TCP) is used by gastroenterologists. We currently use the term tropical calcific pancreatitis (TCP) to denote the pre-diabetic stage of FCPD for which we have also coined the term "pre-FCPD" as shown in Figure 1 (2,3).

Historical background and prevalence

In 1959, Zuidema's (4) landmark paper reported on a series of 45 cases with pancreatic calcification from Indonesia. Zuidema's patients were very poor and consumed a diet deficient in calories and protein. Non-ketotic diabetes mellitus of a severe degree was seen in 16 of 18 patients and insulin resistance were additional features. Marked emaciation, parotid gland enlargement, and hair and skin changes resembling kwashiorkor were the striking clinical features. Reports from several

tropical parts of the world (5-11) have confirmed the widespread occurrence of this syndrome in several developing countries of the world, mostly located in the tropical zone.

The single largest series of cases of (FCPD) reported to date is from the southwestern state of Kerala in India, where Geevarghese (12,13) and Pitchumoni (14,15) observed this disease in endemic proportions in two major medical college hospitals. Indeed, Geevarghese collected one of the largest series in the world (over 1700 patients) and two monograms on the subject were published by him (12,13) and is therefore often referred to as "Father of Pancreatic Diabetes". The clinical features of FCPD and tropical chronic pancreatitis have also been described by other workers in Kerala (16-20), Orissa (21-23), Karnataka (24), Tamil Nadu (25-28), Nagpur (29), Tripura (30) and other places in India (31).

At the M.V. Diabetes Specialities Centre (MVDSC) at Chennai, (formerly Madras) a large referral centre for diabetes in Tamil Nadu state in south India, approximately 50 patients with FCPD are registered annually, which constitutes about 0.7% of all diabetic patients. The distribution of type of diabetes seen at our centre is shown in Table 1. A total of 913 patients with chronic pancreatitis have been registered at our centre of which FCPD consists 624, TCP without diabetes 76, alcoholic chronic pancreatitis 183 and other types 30.

Table 1: Distribution of types of diabetes seen at our centre (n=89180)

Variants	Number	Percentage
Type 2 diabetes mellitus	85163	95.5
Type 1 diabetes mellitus	1365	1.53
Fibrocalculous pancreatic diabetes	624	0.7
Others	2028	2.3
TOTAL	89180	100

Clinical presentation

FCPD patients present with several distinct clinical features. Earlier reports suggested that patients were poor, extremely emaciated, young (over

90% are below 40 years of age at onset), and emphasised the presence of protein calorie malnutrition, bilateral parotid enlargement, distended abdomen and sometimes a cyanotic hue of the lips. However, recent reports suggest a change in the clinical presentation that may be attributed to improved nutritional status. We found that while the majority of patients were lean, severe malnutrition was uncommon, many patients were of ideal body weight (36) and an occasional patient even obese (32). Most of the patients are aged 10-30 years when the diagnosis is made, but FCPD may occur in infancy (33), childhood (34) and the elderly (35). The clinical picture of FCPD consists of the following four cardinal features:

- Abdominal pain (36-39)
- Pancreatic calculi (40)
- Maldigestion leading to steatorrhoea (41) and
- Diabetes

However all features need not be present in every patient.

This article will mainly focus on the diabetes aspects as several other authors will be describing the exocrine aspects of the disease.

Diabetes

Diabetes is an inevitable consequence of the disease, commonly occurring a decade or two after the first episode of abdominal pain (38,39). In lean and undernourished individuals, the diabetes tends to be more severe and polyuria and polydipsia are the major presenting complaints. In the better nourished patients, the symptoms may be insidious and the diagnosis of FCPD is usually made during investigations for pain in the abdomen. Unless there is a high index of suspicion, the diagnosis is often delayed or missed. One of the characteristic clinical features of FCPD is that despite requiring insulin for control, patients rarely become ketotic on withdrawal of insulin. This is attributed to the following factors:

1. Partial preservation of beta cell function as shown by C-peptide studies (42-45).
2. Decreased glucagon reserve (46).

3. Reduced supply of non-esterified fatty acid (NEFA), the fuel needed for ketogenesis, due to the loss of subcutaneous tissue.
4. Resistance of subcutaneous adipose tissue lipolysis to epinephrine.
5. Carnitine deficiency, affecting transfer of NEFA across mitochondrial membrane (47).

While some studies have shown that patients with FCPD have insulin resistance to a similar degree to that seen in type 2 diabetic patients (48), others have not found insulin resistance to be a major factor in FCPD (49).
Diabetes is usually very severe with a fasting blood glucose from 11.1–22.2 mmol/l (200–400 mg/dl) and often requires the use of insulin for control. The mean daily insulin dose in a clinic based study was 40 ± 12 units/day when oral hypoglycemic agents were also used (49,50). However there is a wide spectrum in the clinical presentation of FCPD with patients requiring only diet/oral drug treatment at one end of the spectrum to others who present with ketosis requiring insulin for survival at the other end (Figure 2).

Pathology

FCPD is a progressive disease. Therefore the pathological findings depend on the stage of the disease at which the specimen is obtained. The pathological changes in FCPD are mostly reported from postmortem or surgical specimens and hence represent very late stages of the disease based on which several excellent reviews have been published (51-53) and hence the gross findings and microscopic findings are not discussed here and only brief mention of the immunohistochemistry will be done.

Immunohistochemistry

Immunohistochemistry has shown paucity of alpha cells and beta cells with a decrease in the number of islets in some cases and hyperplasia in others (52,54). Nesidioblastosis may also be present in some patients (Figure 3). There is an overall decrease in insulin positivity in the islets which often correlates with the serum c-peptide levels and inversely with the duration of diabetes (54).

Etiology and pathogenesis

The etiopathogenetic mechanisms of FCPD still remain unclear. There is no satisfactory experimental model for FCPD. The following hypotheses have been proposed based on epidemiological data:

1. Malnutrition theory
2. The cassava hypothesis and other dietary toxins
3. Oxidant stress hypothesis and trace element deficiency states.
4. Familial and genetic factors

The first three have been reviewed extensively (55-57) and hence have not been discussed here. I shall therefore briefly touch upon the familial and genetic factors where some new data has emerged.

Familial aggregation of FCPD

FCPD sometimes affects many members of the same family. One study (58) found 17 families with two or more members having evidence of pancreatitis. In a more recent study, nearly 8% of patients with FCPD were shown to have evidence of a familial aggregation (59). However, many patients also had a family history of Type 2 diabetes. In some families, there was evidence of vertical transmission of FCPD from the parents to the offspring, while in others, there was horizontal distribution of the disease among siblings. Familial aggregation suggests, but does not necessarily prove, a hereditary etiology for FCPD, since several family members could arguably be exposed to the same toxic or other environmental factors. However recent studies suggest that there is a genetic predisposition to FCPD (see below).

Genetic factors

Whatever be the nutritional or toxic factor that predisposes to FCPD, it is clear that only a minority of people exposed to the risk seem to get the disease, suggesting a possible role for genetic factors in the causation of the disease. Our group was the first to suggest a genetic susceptibility to FCPD and in that report we found that FCPD shares common susceptibility genes with both Type 1 and Type 2 diabetes (60).

Many subsequent studies have looked for genetic abnormalities in all forms of chronic pancreatitis following the discovery of genetic mutations in hereditary pancreatitis (60-62). We reported no association between FCPD and the reg gene or the trypsinogen gene (63). In a previous study on a small cohort of patients with tropical pancreatitis, the frequency of CFTR mutations was lower than in white subjects (64). However during the last 2-3 years, a number of independent groups have confirmed an association between SPINK 1 mutations and FCPD (65-67).

SPINK 1 mutations

In the normal pancreas, a number of mechanisms work synergistically preventing the premature activation of trypsinogen to trypsin. The central mechanism of acinar cell injury is autodigestion by active trypsin. Pancreatic secretory trypsin inhibitor (PSTI / SPINK 1) is a potent protease inhibitor and thought to be a major protective mechanism preventing inappropriate activation of pancreatic digestive ensyme cascade by inhibiting upto 20% of potential trypsin activity. Mutations of SPINK 1 gene are significantly associated with tropical calcific pancreatitis as demonstrated by Chandak et al (65). Their studies revealed that the frequency of SPINK1 mutations are similar in both TCP and FCPD patients showing that they are probably the same disease.

SPINK 1 mutations was also studied in FCPD subjects from Chennai and Dhaka (66). In the total study group (Bangladeshi and Southern Indian) the N34S variant was present in 33% of 180 subjects with FCPD, 4.4% in non-diabetic subjects and 3.7% in Type 2 diabetes. These results suggest that the N34S variant of SPINK 1 is a susceptible gene for FCPD Bhatia et al (67) also found a strong association with SPINK 1 trypsin inhibitor mutations and a high prevalence of N34S in FCPD and TCP again suggesting that both entities have similar genetic predisposition.

Investigations

Diagnosis of FCPD is made by establishing evidence of chronic pancreatitis in patients who have the typical clinical features described earlier. If pancreatic calculi are present on plain abdominal radiography, the diagnosis is straightforward. Unfortunately, there are still no sensitive and specific non-invasive blood or urine tests to diagnose early stages of chronic pancreatitis. As in other types of chronic pancreatitis, the diagnosis of FCPD

is seldom made in the early stages of the disease. The investigation for a suspected case of FCPD without pancreatic calculi is as follows:

Tests of pancreatic structure

a. Ultrasonography

b. Computed tomography

c. Endoscopic retrograde cholangiopancreatography

d. Endoscopic ultrasonography

e. Tests of pancreatic function

Test of Pancreatic Function

1. Tests of exocrine pancreatic function
2. Tests of endocrine pancreatic function.

As most of these sections will be covered by gastroenterologists, the derangement of endocrine function will be discussed here.

Endocrine function

Studies on C-peptide assay (a marker of pancreatic beta cell function) in FCPD patients indicate partial preservation of pancreatic beta cell function, in contrast to classical type 1 patients who have negligible beta cell reserve. Yajnik et al (68) measured beta cell function in TCP patients with different degrees of glucose tolerance and found that plasma C-peptide concentrations were normal in those with normal or mildly impaired glucose tolerance.

In the diabetic group, the C-peptide levels were scattered: they were severely diminished in some while in the rest some beta cell reserve was present. Plasma glucagon responses have been shown to be blunted in patients with FCPD (46). In response to a glucose load, plasma glucagon levels rose sharply in subjects with primary forms of diabetes, whereas glucagon response was absent in the FCPD group.

Complications

Complications secondary to chronic pancreatitis

Complications due to chronic pancreatitis include pseudocysts, pancreatic abscesses, and ascites. Obstructive jaundice may also be occasionally seen, which can be due to common bile duct obstruction or associated carcinoma of the pancreas. This is not discussed further here.

Complications related to diabetes

It was earlier believed that patients with FCPD do not develop long term complications of diabetes. This belief was based mainly on the assumption that being a secondary form of diabetes, patients with FCPD do not live long enough to develop specific diabetes related complications, which normally set in only after 10–15 years of diabetes. However, a series of studies from our group and others have shown that both microvascular and macrovascular complications do occur in patients with FCPD.

Rema et al (69) reported advanced retinopathy in FCPD patients, which has been confirmed by others (70). Nephropathy was seen in 8.9% of our FCPD patients. Renal failure due to diabetic nephropathy has also been reported in other forms of pancreatic diabetes (71). Peripheral neuropathy (72) and autonomic neuropathy (73,74) have also been reported in those with FCPD. Macrovascular complications are, however, rare in FCPD. This is believed to be due to three reasons: the patients are young, lean, and have low lipid levels. However, ischaemic heart disease (75), peripheral vascular disease and cerebrovascular accidents have occasionally been reported (76-79). Recently we did a comparative study on the prevalence of long term complications of diabetes in a large group of FCPD patients and a group of type 2 diabetic patients matched for age, sex, and duration of diabetes. The prevalence of all microvascular complications was found to be equal in both groups but macrovascular complications, particularly coronary heart disease, was significantly lower in the FCPD group (79). The prevalence of complications among the study groups is shown in Table 2.

Table 2: Prevalence of diabetes complications among the study groups (121)

Complication	Type 2 diabetes (n = 277)	FCPD (n = 277)	p value
Coronary artery disease	33 (11.9%)	13 (5.1%)	0.003
Peripheral vascular disease n(%)	12 (4.3%)	13 (4.7%)	NS
Retinopathy n (%)	103 (37.2%)	100 (36.1%)	NS
Neuropathy n (%)	70 (25.3%)	58 (20.9%)	NS
Nephropathy n (%)	42 (15.0%)	30 (10.1%)	NS
Microalbuminuria n (%)	65 (23.5%)	73 (26.4%)	NS

Long term survival analysis

In the 1960s and 70s, it was reported that FCPD patients develop abdominal pain in childhood, diabetes by adolescence, and die of complications of diabetes or chronic pancreatitis by early adulthood. Today, FCPD patients survive much longer, perhaps due to improved nutrition and better control of diabetes. We analysed the survival time of a cohort of 370 FCPD patients, taking the date of first occurrence of abdominal pain and the time of onset of diabetes as the two reference points (80). About 80% of patients were alive 35 years after the first episode of abdominal pain. The mean survival time after the diagnosis of diabetes was 25 years. The majority of deaths were associated with diabetes related causes, with diabetic nephropathy accounting for 40%. Severe infections, pancreatic cancer, and pancreatitis related causes also contribute to the mortality of FCPD patients. However, the overall prognosis of these patients seems to have considerably improved during the last two to three decades.

Natural history

Abdominal pain usually is the first symptom to manifest in the natural history of FCPD. After prolonged periods varying from a few months to several decades, pancreatic calculi may be diagnosed by routine

abdominal radiography. Until this point, both endocrine and exocrine pancreatic function of the subject may be found to be normal.

After some months to years, glucose intolerance and/or exocrine pancreatic dysfunction may set in. Although this is the classical presentation, the first sign of the disease may be detection of pancreatic calculi, diabetes, or steatorrhoea. It is believed by most workers in the field that FCPD is the logical end point of TCP i.e. that TCP is the prediabetic stage of FCPD. However, recent reports from Bangladesh have suggested that TCP and FCPD are two different entities (81,82). Based on long term follow up of large numbers of patients, we believe that FCPD is indeed the later diabetic stage of TCP for the following reasons:

1. TCP patients are younger than FCPD patients (83)
2. TCP patients are also seen at the impaired glucose tolerance stage (83, 84), which is considered to be a prediabetic stage.
3. The presence of SPINK 1 mutations in both TCP and FCPD (67), suggests a common genetic basis.

However, till recently there was no follow up study of patients who were actually followed through to the stage of FCPD. We recently conducted a prospective follow-up study on subjects who had TCP and sex matched controls without TCP (79). Among the subjects with TCP 42.3% (11/26) developed diabetes and 15.4% (4/26) developed IGT on follow-up. Thus, nearly 58% of the TCP patients followed, developed FCPD during the follow-up period compared to 26% of the control subjects. The conversion to diabetes was higher among subjects with more severe exocrine dysfunction, as assessed by lower faecal chymotrypsin levels. It was also found that early surgical intervention prevented progression to diabetes.

Management

a. Diabetes: The basic principles of diet and exercise are the same as for the other types of diabetes except that a more liberal calorie and protein intake may be advised because of the associated

undernutrition. Oral hypoglycemic agents may be useful in cases with mild diabetes and relatively early in the course of the disease. However, the majority of patients eventually need insulin for control of diabetes and to improve their general health and sense of well-being.

b. Steatorrhea: Pancreatic enzymes help to reduce steatorrhoea and also improve quality of life (85). They may occasionally help to improve diabetic control and abdominal pain.

Conclusions

FCPD is a unique form of diabetes secondary to tropical calcific pancreatitis[86]. Work during the last 2-3 decades has thrown considerable light on the clinical features and natural history of his condition. This has also led to improved survival of these patients. However, the etiology still remains a mystery and more work needs to be done on this in the future.

Acknowledgement

Dr. Mohan wishes to place on record the tremendous support received from his numerous collaborators in India and abroad for the various studies conducted by him over two decades from 1981 to 2004. The author has published more than 60 articles on this subject. A full bibliography is available at our website **www.mvdsc.org**.

Fig. 1: Natural history of FCPD showing TCP (Pre-FCPD) and FCPD stages of the disease. Reproduced with permission from publishers (Ref.86).

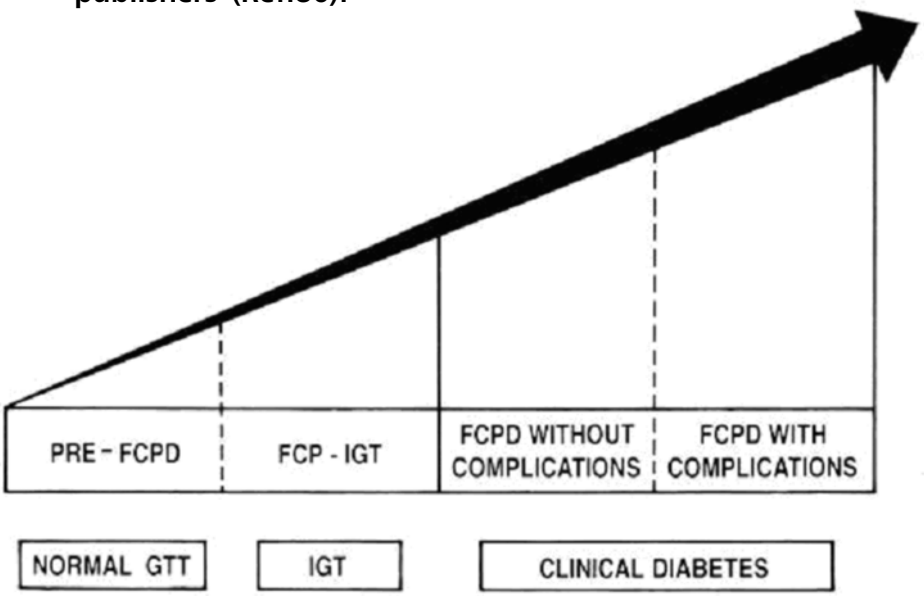


Fig. 2: Clinical spectrum of severity of FCPD: OHA (oral hypoglycemic agents). Reproduced with permission from publishers (Ref.2).

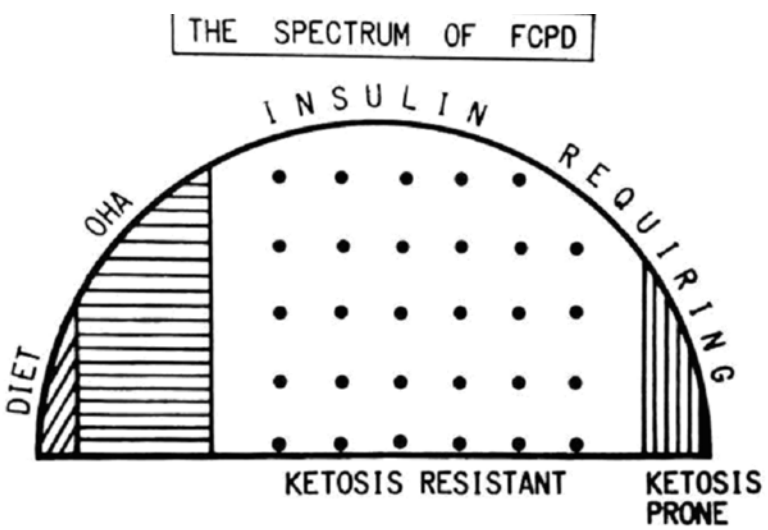
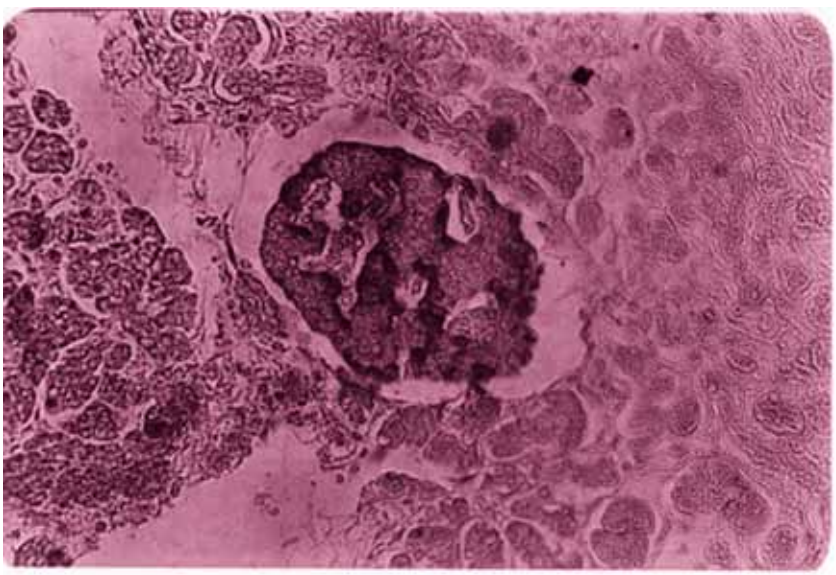


Fig. 3: Histopathology showing "nesiodioblastosis" from a case of fibrocalculous pancreatic diabetes, showing islet tissue arising from ductal remnants (aminoethylcarbazole stain; magnification x40).



References

1. WHO study group report on diabetes mellitus. WHO Technical Report series No.727. Geneva: WHO, 1985.
2. Mohan V, Alberti KGMM. Diabetes in the tropics. In: Alberti KGMM, Defronzo RA, Keen H, Zimmet P, eds. International Textbook of Diabetes Mellitus. Chichester, John Wiley and Sons Ltd., 1997, pp.177-196.
3. Mohan V, Premalatha G. Fibrocalculous Pancreatic Diabetes. Int. J. Diabetes. 1995; 3: 71-82.
4. Zuidema PJ: Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Geog Med 1959; 11:70-74.
5. Shaper G: Chronic pancreatic disease and protein malnutrition. Lancet 1960; ii:1223:1224.
6. Kinnear TWA: Patterns of diabetes in a Nigerian teaching hospital. W Afr Med J 1963; 40: 228-233.
7. Mngola EN: Diabetes Mellitus in the African enviornment - the dilemma. In: Mngola EN, ed. Diabetes 1982. Proceedings of the II Congress of the IDF. Amsterdam, Excerpta Medica, 1983: 309 - 313.
8. Dani R, Penna FJ, Nogueria CED. Etiology of chronic pancreatitis in Brazil: a report of 329 consecutive cases. Int J Med 1976; 316-320.
9. Vannasaeng S, Nitiyanant W, Vachayanat A et al. Characteristics of diabetes with onset under 30 years in Thailand. In: Mimura G, ed. Childhood and Juvenile Diabetes Mellitus, Amsterdam, Excerpta Medica, 1998, pp.75-79.
10. Azad Khan AK, Banik NG and Mahatab H. Malnutrition related diabetes mellitus in Bangladesh, In: Rifkin H, Colwell JA, Taylor SI, eds. ICS 1000, Amsterdam, Excerpta Medica, 1991, pp.944-949.
11. IIlangovekara V. Malnutritiion related diabetes in Sri Lanka fact or fiction ? J Ceylon College of Physicians 1995; 28; 16-225.
12. Geevarghese PJ. Pancreatic Diabetes. Bombay: Popular Prakashan. 1968: 110-105.
13. Geevarghese PJ. Calcific Pancreatitis. Varghese Publishing House, Bombay, 1985.
14. Pitchumoni CS. Special problems of tropical pancreatitis. J. Clin. Gastroenterol. 1985; 13: 941-959.
15. Mohan V, Pitchumoni CS. Tropical Chronic Pancreatitis. In : Beger HG, Warshaw AL, Buchler MW, Carr-Locke DL, Neoptolemos JP, Russell C, Sarr MG eds. The Pancreas (Vol 1), Blackwell Science, London 1998, pp.688-697.
16. Augustine P. Discussion on epidemiology and clinical features of tropical calcific pancreatitis. In: Kumar N, Acharya SK eds. Tropical Calcific Pancreatitis. Trivandrrum, Roussel Scientific Institute, 1997, pp.41-44.
17. Balakrishnan V. Tropical pancreatitis (pancreatic tropicale). In: Bernades P, Hugier M, eds, Maladies du Pancreas Exocrine, Doin, Pairs, 1987, pp.207-227.

18. Mathew Roy VC. Malnutrition related diabetes mellitus – a review. Diabetes Bulletin, Research Society for Study of Diabetes in India. 1996: 7-12.

19. Balakrishnan V, Hariharan M, Sindhu S. Pathogenesis of pancreatitis in India leading on to diabetes mellitus. Proc. Nutr. Soc. India. 1990; 36: 1-7.

20. Pai KN, Ramachandran A. Diabetes mellitus in the endemic pancreatic syndrome of Kerala. In: Kumar V, ed. Disorders of Carbohydrate Metabolism, New Delhi, Arnold Heinmann, 1974, pp.139-150.

21. Tripathy BB, Samal KC. Chronic calcific pancreatitis in the young in Orissa. In: Balakrishnan V, ed. Chronic Pancreatitis in India, Balakrishnan V, (ed), Indian Society of Pancreatology, Trivandrum., 1987, pp 87-96.

22. Tripathy BB. Epidemiology of tropical calcific pancreatitis. In: Kumar N, Acharya SK, eds. Tropical calcific pancreatitis, Trivandrum, Roussel Scientific Institute, 1994, pp.12-28.

23. Tripathy BB, Samal KC. Overview and consensus statement on diabetes in tropical areas. Diabetes/Metab Rev 1997; 13 : 63-76.

24. Nagalotimath SJ. Pancreatic in Karnataka. A note on pathology. In: Balakrishnan V, ed. Chronic pancreatitis in India. Trivandrum, Indian Society of Pancreatology, 1986, pp.105-111.

25. Viswanathan M: Pancreatic Diabetes in India: an overview. In: Podolsky S, Viswanathan M, eds. Secondary Diabetes; the spectrum of diabetic syndromes, New York, Raven Press, 1980:105-116.

26. Mohan V, Mohan R, Susheela L, et al. Tropical pancreatic diabetes in South India.: heterogeneity in clinical and biochemical profile. Diabetologia. 1985; 28:229-232.

27. Moses SGP, Kannan V. The clinical profile of undernourished diabetics aged 30 or less with associated complication in Madras. In: Baba S, Goto Y, and Fukui I, eds. Diabetes Mellitus in Asia, Amsterdam, Excerpta Medica, 1976: 259-262.

28. Mohan V, Chari S. Tropical chronic pancreatitis in South India. In: Recent Advances in Surgery (Eds.) Johnson CD, Taylor I (Eds.) Churchill Livingstone, U.K.,165-179, 1994.

29. Pendsey SP, Doongaji SK, Vaidya MG. Clinical profile of fibrocalculous pancreatic diabetes (FPCD) from Vidarbha region. J Diab Assoc India 1990; 30;7.

30. Bhattacharya PK, Mohan V. Fibrocalculous Pancreatic Diabetes in Tripura. The Antiseptic 1990; 87:161-165.

31. Anand BS. Clinical profile of chronic pancreatitis in Delhi. In: Balakrishnan V, ed. Chronic pancreatitis in India, Trivandrum, Indian Society of pancreatoloty, 1987:15-22.

32. Mohan V, Chari S, Ramachandran A, et al. Fibrocalcific pancreatic diabetes and obesity. Diabetes Res Clin Pract 1990;8:161–166..

33. Premalatha G, Mohan V. Fibrocalculous pancreatic diabetes in infancy—two case reports. Diabetes Res Clin Pract 1990;25:137–140.

34. Mohan V, Ramachandran A, Vishwanathan M. Childhood onset fibrocalculous pancreatic disease. J Assoc Physicians India 1989;37:342–345.

35. Mohan V, Suresh S, Suresh I, et al. Fibrocalculous pancreatic diabetes in the elderly. J Assoc Physicians India 1989;37:342–345.

36. Viswanathan M. Pancreatic diabetes in India: an overview, In: Podolsky S, Viswanathan M, eds. Secondary diabetes: the spectrum of the diabetes syndromes. New York: Raven Press, 1980:105.

37. Balakrishnan V. Chronic calcifying pancreatitis in the tropics. Indian J Gastroenterol 1984;3:65–67.

38. Mohan V, Nagalotimath SJ, Yajnik CS, et al. Fibrocalculous pancreatic diabetes. Diabetes Metab Rev 1998;14:153–170.

39. Mohan V, Pitchumoni CS. Tropical chronic pancreatitis. In: Beger HG, Warshaw AL, Buchler MW, eds. The pancreas. Vol 1. London: Blackwell Science, 1998:688–697.

40. Narendranathan M. Chronic calcific pancreatitis in the tropics. Trop Gastroenterol 1981;2:40–45.

41. Balakrishnan V, Sauniere JH, Hariharan M, et al. Diet, pancreatic function and chronic pancreatitis in South India and France. Pancreas 1988;3:30–35.

42. Mohan V, Snehalatha C, Ramachandran A, et al. Pancreatic beta cell function in tropical pancreatic diabetes. Metabolism 1983;32:1091–1092.

43. Sood R, Ahuja MMS, Karmarkar MG. Serum C-peptide levels in young ketosis resistant diabetics. Indian J Med Res 1983;78:661–664.

44. Vannasaeng S, Nitiyanant TW, Vachayanrat A, et al. C-peptide secretion in calcific tropical pancreatic diabetes. Metabolism 1986;35:814–817.

45. Samal KC, Das S, Parija CR, et al. C-peptide responses to glycaemic stimuli. J Assoc Physicians India 1987;37:362–364.

46. Mohan V, Snehalatha C, Ramachandran A, et al. Plasma glucagon responses in tropical fibrocalculous pancreatic diabetes. Diabetes Res Clin Pract 1990;9:97–101.

47. Yajnik CS, Shelgikar KM, Naik SS, et al. The ketosis resistance in fibrocalculous pancreatic diabetes: clinical observations and endocrine metabolic measurements during oral glucose tolerance test. Diabetes Res Clin Pract 1992;15:149–156.

48. Mohan V, Ramachandran A, Vijaya Kumar G, et al. Insulin resistance in fibrocalculous (tropical) pancreatic diabetes. Horm Metab Res 1988;12:746–748.

49. Mehrotra RN, Bhatia E, Choudhury G. Beta cell function and insulin sensitivity in tropical calcific pancreatitis from North India. Metabolism. 1997;46:441–444.

50. Mohan V, Ahmed MR, Ramachandran A, et al. Clinical profile of tropical pancreatic diabetes at Madras. In: Balakrishnan V, ed. Chronic pancreatitis in India. Trivandrum: Indian Society of Pancreatology, 1987:97–104.

51. Nagalotimath SJ. Pancreatic pathology in pancreatic calcification with diabetes. In: Podolsky S, Viswanathan M, eds. Secondary diabetes: the spectrum of diabetic syndromes. New York: Raven Press, 1980:117–145.

52. Nair B. Pathology of tropical calcific pancreatitis. In: Kumar N, Acharya SK,eds. Tropical calcific pancreatitis. Kerala: Roussel Scientific Institute,1994:83–90.

53. Nair B, Latha P. Pancreas in chronic pancreatitis in India. In: Balakrishnan V, ed. Trivandrum: Indian Society of Pancreatology, 1987:115–120.

54. Govindarajan M, Mohan V, Deepa R, et al. Histopathology and immunohistochemistry of pancreatic islets in fibrocalculous pancreatic diabetes. Diabetes Res Clin Pract 2001;51:29–38.

55. Rao RH, Yajnik CS. Malnutrition related diabetes: time to think? Diabetes Care 1996; 19: 1014-1017.

56. Mathangi DC, Deepa R, Mohan V, Govindarajan M, Namasivayam A. Long term ingestion of Cassava (Tapioca) does not produce diabetes or pancreatitis in the rat model. International Journal of Pancreatology 2000; 27: 203-208.

57. Balakrishnan V. Tropical pancreatitis, epidemiology, pathogeness and etiology. In: Balakrishnan V, ed. Chronic pancreatitis in India, Trivandrrum, Indian Society of Pancreatology, 1987, pp 81-85.

58. Pitchumoni CS. Familial pancreatitis. In: Pai KN, Soman CR, Varghese R, eds. Pancreatic Diabetes. Trivandrum, Geo Printers, 1970: 46-48.

59. Mohan V, Chari S, Hitman GA, et al. Familial aggregation in tropical firbrocalculous pancreatic diabetes. Pancreas 1989; 4: 690-693.

60. Kambo PK, Hitman GA, Mohan V, et al. The genetic predisposition to Fibrocalculous Pancreatic Diabetes. Diabetologia 1989; 32: 45-51.

61. Whitcomb DC. Genetic predisposition to acute and chronic pancreatitis. Med Clin North America 2000; 84: 531-547.

62. Witt H, Luck W, Hennies HC, et al. Mutations in the gene encoding the serien protease inhibitor, kazal type 1 are associated with chronic pancreatitis. Gastroenterology. 2000; 119: 615-623.

63. Hassan Z, Mohan V, McDermott MF, et al. Pancreatitis in fibrocalculous pancreatic diabetes mellitus is not associated with common mutations in the trypsinogen gene. Diabetes / Metabolism Research and Reviews. 2000; 16: 454-457.

64. Bhatia E, Eurie P, Zielenski J, et al. Mutations in the cystic fibrosis transmembrane regulator gene in patients with tropical calcific pancreatitis. Am. J. Gastroenterol. 2000; 95: 3658-3659.

65. Chandak GR, Idris MM, Reddy DN, Bhaskar S, Sriram PVJ, Singh L. Mutations in the pancreatic secretory trypsin inhibitor gene (PSTI/SPINK1) rathern than the cationic trypsinogen gene (PRSSI) are significantly associated with tropical calcific pancreatitis. J Med Genet 2002; 39: 347-351.

66. Hassan Z, Mohan V., Ali L, et al. SPINK 1 is a susceptibility gene for fibrocalculous pancreatic diabetes in subject from the Indian subcontinent. Am J. Hum Genet. 2002; 71: 964-968.

67. Bhatia E, Choudhuri G, Sikora SS, et al. Tropical calcific pancreatitis: strong association with SPINK 1 trypsin inhibitor mutations. Gastroenterology 2002; 123: 1020-1025.

68. Yajnik CS, Shelgikar KM, Sahasrabudhu RA, et al. The spectrum of pancreatic exocrine and endocrine (beta cell) function in tropical calcific pancreatitis. Diabetologia 1990;33:417–421.

69. Rema M, Rajendran B, Ramachandran A, et al. Retinopathy in tropical pancreatic diabetes. Arch Ophthalmol 1985;103:1487–1489.

70. Shelgikar KM, Yajnik CS, Mohan V. Complications in fibrocalculous pancreatic diabetes—the Pune and Madras experience. International Journal of Diabetes in Developing Countries 1995;15:70–75.

71. Levitt NS, Adams G, Salmon J, et al. The prevalence and severity of microvascular complications in pancreatic diabetes and IDDM. Diabetes Care 1995;18:971–974.

72. Ramachandran A, Mohan V, Kumaravel TS, et al. Peripheral neuropathy in tropical pancreatic diabetes. Acta Diabetologica Latina 1985;23:135–140.

73. Govindan R, Das AK. Cardiac autonomic function in fibrocalculous pancreatic diabetes. Acta Diabetol 1993;30:30–36.

74. Mohan V, Sastry NG. Premalatha G. Autonomic dysfunction in non insulin dependent diabetes mellitus and fibrocalculous pancreatic diabetes in South India. Diabet Med 1996;13:1038–1043.

75. Mohan V, Premalatha G, Sastry NG. Ischaemic heart disease in south India. Int J Diab Dev Countries 1995;15:64–69.

76. Sastry NG, Mohan V. Hemiplegia in a patient with fibrocalculous pancreatic diabetes. J Assoc Physicians India 2000;48:1129.

77. Mohan V, Ramachandran A, Viswanathan M. Two case reports of macrovascular complications in fibrocalculous pancreatic diabetes. Acta Diabetol 1989;26:345–349.

78. Chattopadhyay PS, Mukhopadhyay J, Chattopadhyay R, et al. Macrovascular disease is not that uncommon in fibrocalculous pancreatic diabetes (FCPD). Diabetes Care 1994;17:462–463.

79. Barman KK, Padmanabhan M, Premalatha G, et al. Prevalence of diabetic complications with fibrocalculous pancreatic diabetic patietns and type 2 diabetic patients—cross sectional comparative study. Journal of Diabetes and its Complications. 2004; 8: 264-270.

80. Mohan V, Premalatha G, Padma A, et al. Fibrocalculous pancreatic diabetes—long term survival analysis. Diabetes Care 1996;19:1274–8.

81. Rossi L, Pfutzer RH, Parvin S, et al. SPINK1/PSTI mutations are associated with tropical pancreatitis in Bangladesh. Pancreatology 2001;1:242–245.

82. Khan AA, Ali L. Tropical calcific pancreatitis and FCPD in Bangladesh. J Gastroenterol Hepatol 1997;12(June):S48–52.

83. Mohan V, Snehalatha C, Chari ST, et al. Clinical and biochemical studies in the prediabetic phase of tropical calcific pancreatitis. Pancreas 1992;7:109–113.

84. Mohan V, Barman KK, Rajan VS, Deepa R, Chari S. Tropical Calcific Pancreatic diabetes is a pre-diabetic stage of Fibrocalculous Pancreatic Diabetes (FCPD) longitudinal follow-up study. Journal of Gastroenterology and Heptatology. 2004. (in press).

85. Mohan V, Poongothai S, Pitchumoni CS. Oral pancreatic enzyme in the control of diabetes mellitus in tropical calculous pancreatitis. Int J Pancreatol 1998;24:19.

86. Mohan V, Premalatha. Fibrocalculous Pancreatic diabetes: Part I. J. Appl. Med. 1996; 22:793-802.

Chapter 15

Tropical calcific pancreatitis and fibrocalculus pancreatic diabetes in Bangladesh

Z Hassan, L Ali and AK Azad Khan

Summary

Fibrocalculous pancreatic diabetes (FCPD) is recognized as a malnutrition related diabetes. It is a point of debate whether FCPD and tropical calcific pancreatitis (TCP) are two different diseases or different stages of the same disease. In this article the evidence is examined whether FCPD is a distinct disease entity, particularly in the light of the authors' clinical experience and studies on the genetic aspects of this disease.

Introduction

Tropical calcific pancreatitis (TCP) is a distinct form of chronic calcific pancreatitis prevalent almost exclusively in tropical countries of Asia and Africa. A substantial number of patients with TCP presents with a form of diabetes termed as Fibrocalculus Pancreatic Diabetes (FCPD). The etiothogenesis of both pancreatitis and diabetes in these cases are still unclear. In the present review we would present evidence for genetic and environmental contribution in both pancreatitis and diabetes in TCP and FCPD.

Tropical Calcific Pancreatitis (TCP)

The disease is not common, but neither rare, in gastroenterological practices in Bangladesh. The patients are typically young, presenting age usually below 30 years, and there is slight male preponderance which may be more apparent than real. Severe abdominal pain is the predominant presenting symptom; in addition, the patients present with various gastrointestinal disturbances.

Pancreatic morphology of the TCP patients has been assessed with plain X-ray, ultrasonography and ERCP. Pancreatic calcification and ductal dilatation- deformity were documented with these techniques. By Axon criteria in ERCP, the ductal damage has been graded as being severe in almost all cases (Rahman et al 2000). Assessment of pancreatic function by the secretin induced bicarbonate output (Rossi et al 2004) and by fecal elastase-1 (Ali et al 2001) echoes the findings of morphological investigations.

TCP patients, by definition, have normal blood glucose both in fasting and postprandial states, their insulin/C-peptide levels are also found to be comparable to control (Rahman et al 2000; Ali et al 2001).

One crucial issue is the differentiation of this group from the alcoholic pancreatitis seen in the western world. Much younger age group, characteristic feature of the stone (large intraductal calculi) ductal deformity (grossly enlarged pancreatic duct), and severity of pancreatic damage at an early stage in TCP is usually sufficient to distinguish it from alcoholic pancreatitis. A more confirmatory evidence would be the involvement of different genes in the respective diseases. It has been demonstrated that about 20% of TCP cases have SPINK1 N34S mutation (Schneider et al 2002) and this has not been found in alcoholic pancreatitis. This, not denying the possible involvement of other genes, conclusively shows that TCP is an entity distinct from alcoholic pancreatitis.

Fibrocalculus Pancreatic Diabetes (FCPD)

For the purpose of the present discussion FCPD is being treated as the diabetic counterpart of TCP, but their interrelation is still uncertain. The presenting age of FCPD is even younger than that of TCP and the patients mainly come to the physicians for diabetes related symptoms. Sometimes, the pancreatic stones are accidentally discovered on plain X-ray/UCG. The morphological feature of the pancreas are almost similar to those of TCP except in 10–20% cases (who are mostly early FCPD cases) in whom the pancreatic damage may be moderate rather than severe (Rahman et al 2000). Pancreatic function shows gross compromise in both the groups (Ali et al 2001).

In contrast to exocrine pancreatic function the endocrine function show dramatic differences in TCP and FCPD subjects. An FCPD patient has very low and, in many cases only residual, insulin/C-peptide in fasting plasma and even with such levels they normally remain nonketotic although their presenting blood glucose level may be quite high (fasting usually >16 mmol/l). The B cell function of these patients has been assessed by glucagon and arginine stimulation (Rossi et al 2004), the conclusion, however, remained the same. Again, exploration of the pancreatitis genes were important in such cases and SPINK1 N34S

mutation has been found in about 55% and 32% FCPD in two different studies (Schneider et al 2002; Hassan et al 2002). This indicates a genetic similarity of FCPD with TCP, however additional gene and environmental factors must be involved in case of FCPD.

Nature of diabetes is a crucial and controversial issue in FCPD. In 1985 the WHO Expert Committee grouped the FCPD as a subclass of malnutrition related diabetes mellitus (MRDM) (WHO 1985), but in the etiological classification of 1999 it was grouped as a disease of the exocrine pancreas (signifying that it is a secondary diabetes) under the major class of other specific types (WHO 1999): American Diabetes Association (ADA) also holds a similar opinion (ADA 1997). Younger age of onset in general and lack of straightforward correspondence between exocrine and endocrine pancreatic damage (Rahman et al 2000) do not support this view. Particularly the near normal plasma glucagon level and the persistence of arginine stimulated glucagon response in FCPD provide strong evidences that diabetes in FCPD is just not similar to a straightforward secondary diabetes like alcoholic pancreatitis where glucagon response is blunted.

Further exploration on the primary nature of diabetes in FCPD reveals a type 1 like feature in around 20% case as substantiated by anti-GAD and IA-2 positivty (Hassan et al 2005). INS VNTR typing did not show significant preferential allele transmission and HLA-DQB1 shows significant association, ie increased transmission of HLA-DQ0302 and decreased transmission of HLA-DQ0202 (Chowdhury et al 2002).

Conclusions

Exploration of gene-environment interaction seems to be the next obvious step to clarify both the nature of pancreatitis and diabetes in TCP and FCPD. While some progress has been made in the genetic aspects, almost no progress could be made to identify the environmental factors. A preliminary study in the western half of Bangladesh indicates a north-south gradient in the prevalence of FCPD and this may indicate a possible link with geographical and cultural factors (as the population is genetically homogeneous). However, large scale community based studies, using the genetic, biochemical and epidemiological instruments, are now needed in this area.

References

1. ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diab Care 1997; **20:** 1183–1197.

2. Ali MS, Ali L, Hassan Z, Sattar, Hasan M Azad Khan AK. Exocrine and endocrine pancreatic functions in tropical calcific pancreatitis and fibrocalculus pancreatic diabetes. Mymenshin Med J 2001; **10**: 23-28.

3. Chowdhury ZM, McDermott MF, Davey S, Hassan Z, Sinnott PJ, Hemmatpour SK et al. Genetic susceptibility to fibrocalculous pancreatic diabetes in Bangladeshi subjects: a family study. Genes Immun 2002; **3**: 5-8.

4. Hassan Z, Mohan V, Ali L, Allotey R, Barakat K, Faruque MO et al. SPINK1 is a susceptibility gene for fibrocalculous pancreatic diabetes in subjects from the Indian subcontinent. Am J Hum Genet 2002; **71**: 964-968.

5. Hassan Z, Hawa MI, Faruque MO, Azad K, Leslie RDG, Azad Khan AK et al. Prevalence of type 1 diabetes in a Bangladeshi population based on the presence of GAD and IA2 antibody. Diabetologia 2005; **48** (Suppl 1): A 55.

6. Rahman MH, Hassan Z, Chowdhury NS, Hasan M, Azad Khan AK and Ali L. Endocrine dysfunction and pancreatic ductal damage in tropical calcific pancreatitis and early fibrocalculous pancreatic diabetes. Diab Res 2000; 35: 61-68.

7. Rossi L, Parvin S, Hassan Z, Hildebrand P, Keller U, Ali L et al. Diabetes mellitus in Tropical Chronic Pancreatitis Is Not Just a Secondary Type of Diabetes. Pancreatology 2004; **4**: 461-467.

8. Schneider A, Suman A, Rossi L, Barmada MM, Beglinger C, Parvin S et al. SPINK1/PSTI mutations are associated with tropical pancreatitis and type II diabetes mellitus in Bangladesh. Gastroenterology 2002; **123**:1026-1030.

9. WHO: Diabetes Mellitus: Report of a WHO Study Group. Geneva: WHO, 1985. Technical Report Series 727.

10. WHO: Report of a WHO Consultation- Definition, Diagnosis and Classification of Diabetes Mellitus. Report of a WHO Consultation, Part I: Diagnosis and Classification of Diabetes Mellitus. Geneva: WHO, NCDS, 1999.

Chapter 16

Fibrocalculous pancreatic diabetes as currently seen in Lucknow, Uttar Pradesh

Eesh Bhatia

Summary

Eighty consecutive FCPD subjects were evaluated for their nutritional status, clinical presentation, b-cell (fasting C-peptide) and exocrine function (fecal chymotrypsin). All patients diagnosed between 1994-2000 (n=32) were followed prospectively for weight gain and glycemic control. Only 20% of patients were of lower socio-economic status, while 55% had a low body mass index (<18 kg/m^2). At onset of diabetes, only 26 (33%) presented with severe insulin-requiring diabetes. Subjects had a wide range of fasting serum C-peptide (0.03-0.76 nmol/l); C-peptide was negatively associated with duration of diabetes (r = -0.48, p=0.001). Fecal chymotrypsin was severely decreased (1.2$\pm$3.2 u/g, normal >8.4 u/g), but did not correlate with C-peptide. Of the 50 patients on whom current data was available, 6 (12%) had died. On prospective follow-up (mean 2.3 years), there was a significant improvement in body mass index (19.4$\pm$2.9 kg/m^2 vs. 17.0$\pm$ 3.7 kg/m^2, p<0.001) and hemoglobin A1c (6.4$\pm$1.6% vs. 8.0$\pm$3.0%, p<0.001). FCPD patients in this study differed from those described in earlier reports in many respects, including improved nutritional status, a wider range of clinical presentation and b-cell function, and a more favorable prognosis.

Introduction

In the Indian sub-continent, fibro-calculous pancreatic diabetes (FCPD) was originally described from Kerala and subsequently other south Indian states. More recently, it has been described from all parts of the country. The disease as we see it has evolved considerably from earlier clinical presentations where subjects presented an early age, had marked emaciation, severe hyperglycemia and a very poor prognosis ((1, 6-8, 10, 14, 15). More recent studies have shown a later age of onset, much better nutritional status, wide range of glucose tolerance and an improved prognosis. The cause for this changed spectrum of the disease is not clear. Is it a result of changes in nutrition, improved health facilities and economic status of the population? Or is it attributable to the fact that genetic and/or environmental factors, which predispose to the illness, are different?

In the current presentation, the clinical features of (mainly middle class) patients with FCPD presenting to a tertiary care center in Lucknow, Uttar Pradesh are delineated and a brief comparison is made with previous studies from different parts of India over past few decades. Earlier reports described the disease as occurring among young adults of a poor socio-economic status.

Patients and methods

Patients

Eighty consecutive patients of FCPD who presented to our hospital (Endocrinology, Gastroenterology or Surgical Gastroenterology services) from1989 to 2000 were included in the study. Of these, 5 patients were related and belonged to 2 families. FCPD was diagnosed on the basis of abdominal pain, pancreatic ductal calcification and diabetes mellitus (WHO criteria, 1985) (17). Subjects with a history of alcohol intake or having obstructive biliary tract disease or hypercalcemia on investigations were excluded.

All the patients belonged to the north Indian state of Uttar Pradesh or adjacent regions. In addition to patients with a classical history of abdominal pain and/or steatorrhoea, we screened all patients with onset of diabetes <30 years by ultrasonographic examination of the pancreas. Also, all patients diagnosed to have tropical calcific pancreatitis without prior evidence of diabetes underwent an oral glucose tolerance test (OGTT).

Clinical features of 97 patients with type 1 diabetes, seen in the Endocrinology department during the same time period, were used for comparison with FCPD subjects.

Clinical evaluation

Patients were evaluated at the time of presentation for their nutritional status (body mass index (BMI), clinical signs of malnutrition, serum albumin). Evaluation for microvascular complications was performed annually. Fundus examination was performed by direct ophthalmoscopy by a trained ophthalmologist. Retinopathy was classified as background

(non-proliferative) or proliferative. Nephropathy was diagnosed if urine dipstick test was positive for protein (subsequently confirmed by 24 hour urine protein >0.5 gm), or if serum creatinine was $\geq$150 mmol/l. Peripheral neuropathy was defined as bilateral absence of ankle jerks and/or objective evidence of sensory loss in the lower extremities. Glycemic control was assessed by hemoglobin A1c (HbA1c), and b-cell function by measuring fasting C-peptide. Exocrine pancreatic function was estimated by faecal chymotrypsin.

Follow up

All patients diagnosed between 1994 and 2000 (n=32) were followed prospectively for their nutritional status, glycemic control and ability to return to their previous occupation. The mean duration of follow-up was 3.2 years (range 1 month – 6 years).

Investigations

Hemoglobin A1c was measured by ion-exchange chromatography (Biorad, Hercules, California). The normal range was 4-6%. Fasting C-peptide was measured by radioimmunoassay (Diagnostic Systems Laboratory, Webster, Texas). Faecal chymotrypsin was measured using an enzymatic technique (Boehringer Mannheim, Mannheim, Germany).

Statistics

The results were expressed as mean $\pm$ SD. Continuous variables were compared by the Student's t-test and categorical variables by the chi-square test or Fisher's exact test. Follow-up data was analyzed by the paired t-test. Correlation between variables was computed using Pearson's correlation coefficient. A two tailed p value <0.05 was considered to be significant.

Results

Demographic Data

Thirty percent of the patients were of rural background. The patients

were evenly distributed throughout the state, with no region having a clustering of cases. There was a male preponderance (53:27). Only 20% of the patients belonged to poor socio-economic strata (monthly family income <1,500 rupees). None of the patients gave a history of consuming cassava in their diet.

Clinical features

Abdominal pain was present in 68 (85%) cases. The onset of pain was always prior to the detection of diabetes. The mean age at onset of diabetes was 27.1±10.1 years (range 11-60 years), with 76% of subjects having an onset <30 years. In comparison, patients with type 1 diabetes had an earlier age at the onset of diabetes (13.3±7.1 years, p<0.001, Table 1)

Table 1: A comparison between clinical features of patients with FCPD and type 1 diabetes

	Type 1 Diabetes	FCPD	P Value
Age (years)	15.9±9.0	31.0±11.1	<0.001
Onset of diabetes (years)	13.3±7.1	27.1±10.1	<0.001
Duration of diabetes (years)	2.6±4.3	4.0±5.0	0.054
BMI (kg/m^2)	17.1±4.4	17.9±3.1	0.17
Serum albumin (g/l)	-	38±7 (n=57)	-
HbA1c (%) (normal range 4%-6%)	8.9±3.2	8.1±3.1	0.23
Fasting serum C-peptide (nmol/l)	0.17±0.15 (n=22)	0.29±0.20 (n=44)	0.014
Ketosis	59/84 (70%)	10/80 (12%)	<0.001

Note: Values are as Mean ± SD.FCPD: fibrocalculous pancreatic diabetes; BMI: body mass index; HbA1c: hemoglobin A1c

The mean BMI at presentation was 17.9±3.1 kg/m^2 (range 10.5-24.5 kg/m^2). A low BMI (< 18 kg/m^2) was found in 55% of FCPD patients, while serum albumin was diminished (<35 g/l) in 26% of patients. None of the patients had parotid gland enlargement, a cyanotic hue or

nutritional edema. Subjects with low BMI had a significantly shorter duration of pain compared to those with normal BMI (8.6 $\pm$ 7.7 years vs. 13.7 $\pm$ 10.5 years, $p<0.05$); however, they could not be differentiated on the basis of their socio-economic status, hemoglobin A1c, C-peptide or fecal chymotrypsin levels.

At the time of diagnosis of diabetes, hyperglycemia was of variable severity. Fifty four (67%) patients were controlled with diet or oral hypoglycemic agents, including 9 (12%) patients who were asymptomatic and diagnosed after an OGTT. At the other end of the clinical spectrum, 26 (33%) patients presented with severe insulin-requiring diabetes, though only 2 patients had ketosis at onset. Of the 54 patients on diet/oral hypoglycemic agents at diagnosis, 24 subjects had a duration of diabetes >5 years when they presented to our hospital. Twenty of these 24 patients (83%) required insulin injections for glycemic control. Patients requiring diet/oral hypoglycemic agents at onset could be differentiated from subjects treated with insulin by an later age at onset of diabetes, and lower plasma glucose and HbA1c (Table 2). However fasting serum C-peptide in the two groups did not differ.

Table 2: Comparison between FCPD patients treated with insulin versus diet/oral agents

	Diet/OHA	Insulin	P value
N	54	26	
Age at onset of diabetes (years)	28.7$\pm$10.6	23.7$\pm$8.3	0.04
Age of onset of pain (years)	19.7$\pm$8.6	17.0$\pm$8.8	0.23
Duration of diabetes (years)	3.8$\pm$4.3	4.3$\pm$6.3	0.67
Gap between pain and diabetes (years)	9.0$\pm$8.9	7.6$\pm$6.3	0.48
BMI (kg/m^2)	18.1$\pm$2.9	17.4$\pm$3.6	0.38
Plasma glucose at onset (mmol/l)	15.7$\pm$6.0	20.3$\pm$5.6	0.01
HbA1c (%)	7.3$\pm$2.6	9.7$\pm$3.8	0.005
Fasting serum C-peptide (nmol/l)	0.30$\pm$0.18 (n=29)	0.22$\pm$0.14 (n=15)	0.12

Note: Values are as Mean $\pm$ SD.FCPD: fibrocalculous pancreatic diabetes; HbA1c: hemoglobin A1c, BMI: body mass index.

Family history

A history of type 2 diabetes was present in first-degree relatives in 36% of patients. Eight (10%) patients had family history of tropical calcific pancreatitis.

β-cell and exocrine function

FCPD patients presented with a wide range of fasting serum C-peptide (0.03-0.76 nmol/l). C-peptide levels were higher compared to subjects with type 1 diabetes (Table 1). Fasting C-peptide showed a positive correlation with BMI ($r=0.42$, $p=0.004$), and a negative correlation with duration of diabetes ($r=-0.48$, $p= 0.001$). Fecal chymotrypsin was severely diminished (1.2 ± 3.2 U/g of stool, normal >8.4 U/g; $n=62$). Chymotrypsin levels were not related to duration of pancreatitis or to fasting C-peptide.

Complications

Twelve patients (15%) had diabetic retinopathy (10 with background and 2 with proliferative changes). Nephropathy was present in 15 (19%) subjects, while 21 (26%) had peripheral neuropathy. No patient with duration of diabetes < 2 years had any microvascular complications.

Mortality

Of the 50 (63%) patients on whom current information was available, 6 (12%) had died. Two patients died due to carcinoma of pancreas, 2 of chronic renal failure secondary to diabetic nephropathy, 1 of cirrhosis related to hepatitis B infection and 1 of septicemia.

Prospective follow up

Subjects ($n=30$) had significant improvement in their nutritional status (BMI 19.4 ± 2.9 kg/m^2 vs. 17.0 ± 3.7 kg/m^2, $p<0.001$); 75% of the patients gained in weight. There was also an improvement in glycemic control (HbA1c $6.4\%\pm1.6\%$ vs. $8.0\%\pm3.0\%$, $p<0.001$). Two patients (6%) died (one due to septicemia and one of chronic renal failure). All patients who were living were able to resume their previous occupation.

Discussion

The patients we have described differ in many respects from the older descriptions of FCPD (1-9, 11-15). In previous reports, the disease occurred predominantly in economically deprived subjects, who were emaciated and suffered from numerous nutritional deficiencies (3-9, 11-15). In contrast, 80% of our patients belonged to a middle or upper income group. Similarly, only a half of our patients had a low BMI, only a third had low serum albumin levels, while parotid gland enlargement and nutritional edema were not encountered. These facts strengthen the hypothesis that protein calorie malnutrition does not play a primary role in the susceptibility to FCPD (1-3, 18). Subjects with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. As in many previous studies (1, 8, 10, 15, 16, 19, 20), intake of cyanogenic glycosides from cassava was not a risk factor in this cohort. There was a high prevalence of chronic pancreatitis in family members, suggesting that genetic factors may be important in its etiology (21).

In contrast to older reports, where most patients at onset had severe insulin-requiring diabetes (1-12, 15), two-thirds of the patients in the current study were initially controlled on diet/oral hypoglycemic agents. Heterogeneity of clinical presentation has also been reported in two recent studies from different regions of India (22, 23). The only clinical characteristics differentiating patients requiring diet/oral hypoglycemic agents or insulin were that the latter were younger, and had worse glycemic control. In contrast to previous reports (22), fasting C-peptide levels did not differ significantly between these two groups of patients.

It has been previously reported that FCPD subjects have markedly diminished C-peptide levels (3, 24, 25). In contrast, in the current study, as well as in other recent studies conducted by others (22, 23, 26), and by our group (27), b-cell function varied widely at presentation. This may reflect the fact that patients now present earlier in the course of their illness. We found that b-cell function was negatively associated with increasing duration of diabetes. This is the likely reason why a large proportion of FCPD patients on diet/oral medications required insulin after 5 years. In their conversion to a state of insulin-dependence over a short time period, these FCPD patients clinically resemble subjects

with slowly progressive type 1 diabetes (28).

In contrast to b-cell function, exocrine function was markedly diminished in all FCPD subjects by the time of presentation. As we have shown previously (16, 27), there was no correlation between fecal chymotrypsin levels and C-peptide levels. While chronic inflammatory changes in the exocrine pancreas may lead to β-cell damage and diabetes, other factors, such as islet cell regeneration (29), may influence the further rate of decline of β-cell function. Our data are in contrast to an earlier study by Yajnik et al (23), which reported that b-cell dysfunction and exocrine function are directly correlated.

It was earlier believed that being a secondary diabetes, microvascular complications might be uncommon in FCPD (5, 8). However, we detected a high prevalence of such complications in this relatively young population. This confirms data from more recent studies from other parts of India (10, 22, 30). Unlike in type 2 diabetes, none of the patients with duration of diabetes <2 years had any microvascular complications. This may reflect the relatively abrupt onset of symptoms of diabetes in FCPD patients.

Patients with FCPD, in addition to having to manage diabetes, also have the burden of complications related to pancreatitis, including recurrent abdominal pain and steatorrhoea. Enzyme supplements are expensive and most of our patients could not afford these on a regular basis. Despite these difficulties, the prospective arm of our study showed that FCPD patients did well on follow-up. Despite having severely diminished fecal chymotrypsin levels, they exhibited a sustained, significant improvement in weight. They also had improvement in their glycemic control with therapy and were able to resume their prior occupations.

In our entire cohort, 6 (12%) patients died, but this figure is likely to be an underestimate since we could not obtain follow-up information on 30 (37%) patients. In our prospective study, only 2 of 30 (6%) patients died. Renal failure and carcinoma of the pancreas were the two most common causes of mortality. This data is similar to a recent study on a large cohort of FCPD patients in which, due to a longer life expectancy

after diagnosis, the two commonest causes of mortality were diabetic nephropathy and pancreatic carcinoma. (31). These data are in contrast to older studies (4), and to more recent study by Yajnik et al (10), where a high mortality rate has been noticed mainly due to infectious diseases, malnutrition and acute diabetes-related complications.

Why is the presentation in the current study different from those reported earlier? Our patients were mainly from the middle-class (rather than from more deprived sections), and are likely to have sought medical advise earlier in the course of their illness. They are likely to have received better medical care compared to that available earlier. Two studies from the same region in south India, conducted more than two decades apart, have reported changes in clinical presentation similar to what we observed (8, 22). This suggests that that genetic heterogeneity is unlikely to be the reason for the observed differences. This conclusion is supported by reports that the genetic predisposition to FCPD appear to be similar in different regions of the subcontinent (32-34)

Our cohort of FCPD patients differed from those described in earliest reports in that they had an improved nutritional status, a varied clinical presentation and course, wide range of beta-cell function, and a relatively good prognosis.

References

1. Barman KK, Premalatha G, Mohan V:Tropical chronic pancreatitis. Postgrad Med J 79: 606-615, 2003
2. Rao RH: Diabetes in the undernourished: coincidence or consequence? Endocrine Rev 9: 67-87, 1988
3. Abu-Bakare A, Taylor R, Gill GV, Alberti KGMM: Tropical or malnutrition-related diabetes: a real syndrome? Lancet i: 1135-1138, 1986
4. Geevarghese PJ: Pancreatic diabetes. Popular Prakashan, Bombay, 1968
5. Geevarghese PJ, Pillai VK, Joseph MP, Pitchumoni CS: The diagnosis of pancreatogenous diabetes mellitus. J Assoc Physicians India 10: 173-180, 1973
6. Shaper AG: Chronic pancreatic disease and protein malnutrition. Lancet i: 1223-1224, 1960
7. Zuidema PJ: Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Geogr Med 11: 70-74,1959
8. Viswanathan M: Pancreatic diabetes in India: an overview. In Secondary diabetes: The spectrum of the diabetic syndromes. Podolsky S, Viswanathan M, Eds. New York, Raven Press, 1980, p. 105-116
9. Chandraprasert S, Samranvej P, Arthanchinta S, Isarena S: Diabetes mellitus and tropical form of chronic calcific pancreatitis in Thailand. Aust N Z J Med 6: 316-320, 1976
10. Yajnik CS, Shelgikar KM: Fibrocalculous pancreatic diabetes in Pune, India. Clinical features and follow-up for 7 years. Diabetes Care 16: 916-921, 1993
11. Nagartnem N, Gunawardene KRW. Aetiological factors in pancreatic calcification in Ceylon. Digestion 5: 9-16, 1972
12. Kinnear TWA: Patterns of diabetes in a Nigerian teaching hospital. W Afr Med J 40: 228-233, 1963
13. McMillan DE, Geevarghese PJ: Dietary cyanide and tropical malnutrition diabetes. Diabetes Care 2: 202-208, 1979
14. Vannasaeng S, Nitiyanant W, Vichayanrat A: Case control study on risk factors associated with fibrocalculous pancreatic diabetes. Diabetic Med 5: 835-839, 1988
15. Tripathy BB, Samal KC: Chronic calcific pancreatitis with diabetes in the young in Orissa. In: Chronic pancreatitis in India: proceedings of a workshop on chronic pancreatitis. Balakrishnan V, Thankappan KR, Eds. Trivandrum, Kerala, St Joseph's Press p. 87-96, 1987
16. Bhatia E, Baijal SS, Kumar R, Choudhuri G: Exocrine pancreatic and b-cell function in malnutrition related diabetes among North Indians. Diabetes Care 18: 1174-1178, 1995

17. World Health Organization. Diabetes Mellitus: report of a WHO study group. World Health Organ Tech Rep Ser 727, 1985

18. Hoet JJ, Tripathy BB: Malnutrition and diabetes in the tropics. Diabetes Care 19:1014-1017, 1996

19. Swai ABM, Mclarty DG, Mtinangi BL Tatala S, Kitange HM, Mlinge N, Rosling H, Howett WP, Brubaker GR, Alberti KGMM. Diabetes is not caused by cassava toxicity. A study in a Tanzanian community. Diabetes Care 15: 1378-1385, 1992

20. Teuscher T, Baillod P, Rosman JB, Teuscher A: Absence of diabetes in a rural West African population with a high carbohydrate/cassava diet. Lancet i: 765-768, 1987

21. Mohan V, Chari ST, Hitman GA, Suresh S, Madanagopalan N, Ramachandran A, Viswanathan M: Familial aggregation in tropical fibrocalculous pancreatic diabetes. Pancreas 4: 690-693, 1989

22. Mohan V, Mohan R, Susheela L, Snehalatha C, Bharani G, Mahajan VK, Ramachandran A, Viswanathan M, Kohner EM: Tropical pancreatic diabetes in south India: heterogeneity in clinical and biochemical profile. Diabetologia 28: 229-232, 1985

23. Yajnik CS, Shelgikar KM, Sahasrabudhe RA, Naik SS, Pai VR, Alberti KGMM, Hockadat TD, Katrak A, Dandona P: The spectrum of pancreatic exocrine and endocrine (beta cell) function in tropical calcific pancreatitis. Diabetologia 33: 417-421, 1990

24. Vannasaeng S, Nitiyanat W, Vichayanrat A, Ploybutr S, Harthong S: C-peptide secretion in calcific tropical pancreatic diabetes. Metabolism 35:814-817, 1986

25. Yajnik CS, Shelgikar KM, Naik SS, Kanitkar SV, Orskov H, Alberti KGMM, Hockaday TDR: The ketosis-resistance in fibro-calculous-pancreatic-diabetes. Clinical observations and endocrine-metabolic measurements during oral glucose tolerance test. Diabetes Res Clin Pract 15,2,149-56, 1992.

26. Yajnik CS, Kanitkar SV, Shelgikar KM, Naik SS, Alberti KGMM, Hockaday TDR: Pancreatic C-peptide response to oral glucose in fibrocalculous pancreatic diabetes. Improvement after treatment. Diabetes Care 13:525-527, 1990

27. Mehrotra RN, Bhatia E, Chouduri G: b-cell function and insulin sensitivity in tropical calcific pancreatitis from North India. Metabolism 46:441-444, 1997

28. Leslie RDG, Pozzilli P. Type 1 diabetes masquerading as type 2 diabetes. Diabetes Care 17, 1214-1219, 1994

29. Govindrajan M, Mohan V, Deepa R, Ashok S, Pitchomoni CS: Histopathology and immunohistochemistry of pancreatic islets in fibrocalculous pancreatic diabetes. Diabetes Res Clin Pract 51, 29-38, 2001

30. Geevarghese PJ, Abraham A: Diagnosis, course and complications. In Calcific pancreatitis and diabetes in the tropics. Geevarghese PJ, Abraham A, Eds. Trivandrum, St Joseph's Press, p 99-107, 1995

31. Mohan V, Premalatha G, Padma A, Chari ST, Pitchumoni CS: Fibrocalculous pancreatic diabetes. Long-term survival analysis. Diabetes Care 19: 1274-1278, 1996.

32. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, Witt H. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. Gastroeneterology 123: 1020-1-25, 2002

33. Schneider A, Suman A, Rossi L, Beglinger C, Parvin S et al. SPINK1/PST1 mutataions are associated with tropical pancreatitis and type 2 diabetes in Bangladesh. Gastroenterology 123: 1026-1030, 2002

34. Chandak GR, Idris MM, Reddy DN, Mani KR, Bhaskar S, Rao GV, Singh L. Absence of PRSS1 mutations and association of SPINK1 trypsin inhibitor mutataions in hereditary and non-hereditary chronic pancreattits. Gut 53:723-728, 2004

Chapter 17

Malnutrition related diabetes mellitus in Orissa

Tripathy BB

Summary

The links between malnutrition and diabetes are fascinating, and this is best exemplified by fibrocalculous pancreatic diabetes. In this article, the genesis of the term is described in detail, as are the associations with malnutrition. The earlier diagnosis of malnutrition-related diabetes mellitus has now given way to malnutrition modulated diabetes mellitus / protein deficient diabetes mellitus; in addition, criteria have been laid down for the diagnosis of the same. In addition, criteria have also been proposed for the diagnosis of fibrocalculous pancreatic diabetes. This article will also focus on the well-known link between malnutrition and diabetes in the state of Orissa, and provide a glimpse of the picture of the disease as seen in Orissa today.

Introduction

The concept of possible role of malnutrition in the genesis and modulation of clinical expression of diabetes mellitus emanated from Orissa. In late 1950s there came reports of young patients with diabetes who had severe hyperglycemia, were very lean and yet did not have ketone in urine. Further, these patients, unresponsive to sulphonylurea compounds, continuously required large doses of insulin for control. This picture did not fit in with juvenile diabetes who are depicted to be ketosis-prone and insulin sensitive so that minor changes in dose of insulin would cause wide alterations in the levels of glucose in blood.

Search into literature revealed description of clinically similar patients by Hugh Jones (1955)[1] from Jamaica. These were classified as J-type as it was not possible to fit them to either type 1 or type 2. None of these patients complained of abdominal pain to raise suspicion of pancreatic disease leading to diabetes. After the presentation by Geevarghese in 1962[2] and my personal discussion with him in 1963, we looked for pancreatic calcification by routine skiagram of abdomen of all such patients to find that some 25% of such patients had a calcific pancreatic disorder. By 1960-61 analysis of patients with features of J-type diabetes had revealed that all of such patients hailed from very poor families living in remote villages, so poor as to be unable to afford two ordinary meals in a day. Nutrition has to be inadequate for the mothers during

pregnancy and for the patients during their infancy and early childhood. This was confirmed by questionnaire method from the guardians of the patients and other family members. The complicity of over-nutrition and obesity with diabetes mellitus is age old. Sushruta (~600 BC) described diabetes in the obese and the indolent. The concept was revived by Bose in 1995[3] and taken up by Joslin in the early decades of the twentieth century.

On the reverse, the association of malnutrition with diabetes was possibly first brought out by Zuidema (1959)[4] from Indonesia, who found pancreatic calcification and diabetes in a group of patients majority of whom suffered from clinically evident protein malnutrition. Shaper (1960)[5] reported similar association from Uganda. Hugh Jones (1955)[1] reviewed 215 patients attending University College Hospital in Jamaica, thirteen of whom could not be classified to either type 1 or type 2. These patients were thin, young, severely hyperglycemic but in contrast to IDDM (type 1) did not have ketonuria and required high dose of insulin for control. He suggested the term 'J' (Jamaica) type for this clinical form of diabetes.

Subsequently (1959-61), similar patients were described from some African, south and South East Asian countries. They were observed only in the poor sections of the respective societies, yet it remained for Tripathy and Kar from Cuttack (Orissa) to implicate early childhood malnutrition as the underlying factor in their presentations in 1963-7[6].

Pathophysiology

The relevance of the hypothesis can be sought from the metabolic changes observed in starvation and malnutrition. Historically glucose intolerance in starvation and vagabond diabetes have been described by researchers such as Claude Bernard and Allen. Minkosky observed greater ease in inducing diabetes in animals on low food uptake. In contemporary literature prediabetic state has been observed in protein deficient litters of dogs and pigs (Heard et al. 1967)[7] and in childhood malnutrition (Baig and Endoziens 1965)[8] and several others[6]. Tripathy, Chhetri and their co-workers separately documented glucose intolerance, hypoinsulinaemia, insulin resistance and high growth

hormone levels in adult patients suffering from clinically evident chronic malnutrition[6]. Malnourished baby monkeys on low protein diet were shown to have similar aberrations by Khardori and Bajaj[9].

Patients with type-J diabetes manifest significant insulinopaenia, high growth hormone and severe insulin resistance[6].

Neel (1962)[10] enunciated his famous dictum "thrifty" genotype rendered detrimental by "progress" as cause of increase in the incidence of diabetes, speculating genetic adaptation of metabolic processes for survival during periods of famine and food deprivation. More recently, Hales and Barker[11] enunciated 'thrifty phenotype' referring to lasting adjustments in the metabolic set up of the fetuses in case of maternal undernutrition as a cause of high susceptibility to diabetes and cardiovascular disease in the offsprings later in life in situations of relative affluence. These observations provide strong support to our concept of the nutritional basis of development of diabetes with atypical presentations when severe undernutrition continues beyond infancy and early childhood as it is not not unusual in a number of developing countries with a proportion of population living far below poverty line. Diabetes develops in those who are otherwise susceptible as in case of some with obesity.

Clinical, experimental and other laboratory data clearly indicate that diabetes evolves primarily from a critical fall in insulin secretion, not from destruction of beta cells as in type 1 diabetes (IDDM) but from functional alteration possibly as an adaptation to nutritional deprivation in the developing phases viz; foetal, infancy and early childhood. This has been corroborated both by mathematical models[12] and autopsy studies[13]. Insulin and C-peptide levels are low, both basal and in response to secretagogues. Long term observations (over 10 years) have revealed absence of decline in b-cell function in J-type diabetes in contrast to type1[6]. The other mechanism involved is insulin resistance observed both in patients with J-type diabetes and chronic mailnutrition[6].

J-type was described as Ketosis Resistant Young Diabetes (KRYD) in the North (Delhi) and Insulin Requiring Diabetes Mellitus (IRDM) in the South (Chemical).On the other hand, young patients with pancreatic calculi

and diabetes were less severely malnourished before onset of diabetes in patients under our observation. In Kerala where incidence was much higher all such patients observed, as belonged to poor families, those subsisting mostly on very low protein containing tapioca (cassava) as staple food. Further these tubers usually boiled and consumed contain cyanogenic glycosides, which have the potential to damage pancreatic constituents as well as the thyroid gland. These findings implicated nutritional deficiency to be involved in the pathogenesis of the condition. Yet I had suggested to Geevarghese not to consider malnutrition as the critical factor, which he has acknowledged in his first monograph published in 1968[14].

Recognition

Global acceptance of the association of malnutrition with diabetes was first expressed by the National Diabetes Data Group (1979)[15] and subsequently corroborated by WHO Expert Committee (1980)[16]. Describing "Special types" of diabetes, the technical report acknowledged two sub type with background of malnutrition viz;

(1) Malnutrition related syndrome of severe non-ketosis diabetes in children in tropics: 'J-type'.

(2) Diabetes with fibrosis and calcification of the pancreas and a history of severe childhood malnutrition and also excessive consumption of cyanide especially from cassava.

These "special classes" were described under other types of clinical diabetes-subhead miscellaneous[16]. In the final classification by WHO Study Group (1985)[17], the position was altered. Next to the well recognized classes (1) IDDM and (2) NIDDM, Malnutrition-related Diabetes Mellitus (MRDM) was placed No. 3 in the classification table. MRDM was further subtyped as (a) Protein-deficient Pancreatic Diabetes (PDPD) and (b) Fibrocalculous Pancreatic Diabetes (FCPD).

Problems

We at Cuttack, Orissa have the opportunity to observe a good number of patients from both these categories. The recognition of our reports

and views were very much welcomed. Yet there were misgivings from two angles.

First the term Protein-deficient PANCREATIC Diabetes was inappropriate, as by the "Experts'" own statement "pancreatic calcification and fibrosis are absent" as also "absence of radiographic or other evidences of intraductal pancreatic calcification or dilatation of the ducts" as well as absence of "demonstrable malabsorption of nutrients caused by exocrine pancreatic insufficiency". The issue was discussed at the VI National Conference on Diabetes held at Cuttack in 1987 and by consensus the name was changed to Protein-Deficient Diabetes Mellitus (PDDM), which was subsequently ratified at the 13th IDF Congress, Sydney (1988).

Secondly, although the term FCPD was considered to be appropriate, its placement in the classification table did not appear to be so. Several groups including our own observed FCPD to occur in individuals in the absence of alcohol intake, gallbladder disease or hyperparathyroid states where malnutrition could be ruled out. Further, as, in the case of FCPD, diabetes occurs in association with florid exocrine pancreatic disorders, to classify it along with primary forms such as IDDM, NIDDM and PDDM was felt to be inappropriate.

MRDM: Clinical features

By and large, patients are below 30 years of age at onset of symptoms. Typically, they are lean even before onset of symptoms and appear poorly nourished. The onset is insidious but may be relatively rapid. Polyuria, polydipsia, asthenia, weakness and cramps often lead to prostration in course of time (months). Hyperglycemia is often quite severe but urine tests negative for ketones. Oral hypoglycemic agents are ineffective. Insulin in relatively high doses is required for control (Fig. 1).

Some such patients may give history of abdominal pain. This is much more often seen in Kerala than elsewhere in India or Bangladesh. X-ray and ultrasonography of abdomen in these patients and some others (without history of distinctive abdominal pain) reveal pancreatic calculi and other features of pancreatic disease (Fig. 2).

Confusion

FCPD, known in gastroenterology circles as Tropical Calcific Pancreatitis has a clear marker, easily brought out by imaging procedures. When onset is at younger age, with little likelihood of alcoholism and gallbladder disease, there can be little doubt about its diagnosis. PDDM on the other hand has to be diagnosed on clinical basis alone. Patients of this type are encountered mainly in charitable general hospitals or in remote rural practice. At many places, there is failure to take note of the atypical features and there is a tendency to overlook or ignore the same. At places where these are noticed, in the absence of a consensus, terms such as ketosis resistant diabetes in young, insulin requiring diabetes mellitus (IRDM), J-type or M (malnutrition) type have been applied. During the 60s and 80s of the last century, distinction between the two types of so called MRDM was blurred particularly in places where both types were not seen in fair numbers. This was the case of Delhi where KRYD was seen almost exclusively and in Madras where FCPD was much more common. Investigators at both places considered J-type as an early, precalcific stage of FCPD.

Controversies continued beyond 1987 as Madras workers suggested that we should agree to differ. It was in the next year that Mohan[18] came out with clear cut criteria required for the diagnosis of FCPD (Table 1), thus squashing the speculations on its identity with PDDM. Further, reports on pancreatic function tests from Cuttack, Delhi, Lucknow, Chennai and Dhaka clearly established pancreatic acinar dysfunction in FCPD and also established the distinction between the two. Moreover, a follow up of several patients diagnosed J-type over 10 years before at Cuttack, established that they remained free from pancreatic exocrine disorder and in contrast to IDDM retained b-cell function over the long period of time[6] (Fig. 3).

Table 1. Diagnostic criteria for FCPD

- Occurrence in a tropical country
- Diabetes by WHO Study Group criteria
- Evidence of chronic pancreatic disease – pancreatic calculi on X-ray or any three of the following:

(a) Abnormal pancreatic morphology with ductal dilatation de tected by sonography, CT scan or ERCP;

(b) Abnormal exocrine pancreatic function tests;

(c) Chronic recurrent abdominal pain since childhood;

(d) Steatorrhoea

Absence of other causes of chronic pancreatitis i.e., alcoholism, hepatobiliary disorder or hyperparathyroidism, etc.

Table 2. Clinical features of PDDM (MMDM)

1. Severe diabetes-fasting blood glucose more than 200 mg/dl
2. Onset of diabetes before the age of 30 years
3. Leanness, Body-mass index $< 18 kg/m^2$
4. Absence of ketosis on withdrawal of insulin
5. Poor socio-economic status, history of childhood malnutrition
6. Insulin requirement more than 60 U/day or more than 1.5 to 2 U/kg/day
7. Of rural origin
8 Absence of radiographic or sonographic findings of pancreatic calculi ductal dilatation and fibrosis; laboratory evidences of exocrine pancreatic dysfunction

The very poor rural background of the patients suggests that they could not have appropriate nourishment during their infancy and early childhood as well as in course of their foetal life. In most cases, dietary history could be ascertained from parents and other accompanying

persons and the diet was found to be utterly deficient.

Height and body weight indicated retardation of growth. Marks of micronutrient deficiency were evident in many cases. High levels of free fatty acids (FFA) and marginal increases in plasma ketones were lower than seen in type 1 diabetes. Insulin and C-peptide levels were somewhat lower at fasting but much more so in response to carbohydrate load, as compared to controls. Growth hormone levels were high and not suppressed by glucose administration[6].

A scoring system for the firm diagnosis of PDDM (MMDM) devised at Cuttack is presented in Table 3.

Table 3. Scoring system for the clinical diagnosis of PDDM (MMDM)

Clinical profile	**Score**
Age at onset 10-30 years	1
Poor economic status (Rural origin)	1
Leanness, BMI < 16 MG/m^2 < 18 mg/m2	2 1
History of malnutrition in childhood	2
Stigmata of malnutrition (clinical) (past or present)	1
Severe hyperglycemia (fasting blood glucose =200 mg/dl)	1
Lack of proneness of ketosis: (absence of ketonuria on withdrawal of insulin for long periods)	3
Insulin requiring over 60 U/day (2 U/day/kg/body weight) unresponsive to suphonylurea compounds	2
Absence of X-ray/ultrasound evidence of pancreatic calculi and ductal dilatation	3
Total score	17
Diagnostic score 13 Suggestive score 12	

FCPD

Most patients seen in the hospital diabetes clinic present with symptoms usual for young patients with diabetes. A small proportion of cases, particularly those seen in private clinics, may have milder symptoms. Another small group of patients have history of abdominal pain and therefore more commonly report to the gastroenterology wing.

Over two thirds of patients attending the hospital are poor compared to 25% of those seeking private consultation. At Cuttack and Chennai, about 10% complain of abdominal pain while another 30% give history of digestive problems on asking leading questions. Mohan's criteria for diagnosis of FCPD (Table 1) have been accepted widely as the most appropriate.

Broad differences between PDDM (MMDM) and FCPD as observed at our center where both types are seen in fair numbers are summarized in table 4.

Table 4. Distinguishing features between PDDM and FCPD (General)

Comparison	**PDDM (MMDM)**	**FCPD**
Age at onset	10-30 years	10-40 years or older
Rural	All	78%
Socioeconomic status: Poor	All (100%)	60%
BMI < 16 kg/m^2	92%	60%
Ketonuria	Nil	16%
C-peptide (2 hour post prandial)	0.6	1.0 pmol/l
Fecal fat (on 100g fat diet/day)	6.2 g/d	29 g/d
Patients presented at the Workshop (1995)		
Mean age	22.1 ± 3.1 yrs	29.8 ± 4.4 yrs
Poor	All	54.5%
History of childhood malnutrition	All	54.5%
Mean BMI (Kg/m^2)	13.7 ± 1.6	15.4 ± 3.1
W/H Ratio	0.7 ± 0.12	0.8 ± 0.07
Fasting blood glucose (mean)	278 ± 79	235 ± 72 mg/dl
Current insulin dose (mean)	78.3 ± 10.4	46.4 ± 12.1 u/d

Despite discussions at several conferences and two international workshops[10, 11] controversies on the term MRDM and its placement along with the two sub classes PDPD and FCPD in the WHO (1985) table of classification remained highly controversial.

It was felt that this situation persisted mostly due to lack of opportunity for diabetologists from other areas to have first hand exposure to clinical material. With the above in view, we planned to hold a workshop at Cuttack, Orissa where contrary to the places of the previous workshops (UK and Japan), typical clinical material could be displayed for observation and analysis.

The workshop held in October 1995, was attended by medical scientists from various specialties covering different aspects of diabetes and nutrition from many nations, viz; USA, UK, Belgium and Sweden. Twelve patients with PDDM and 11 with FCPD were placed before the participants for clinical examination and analysis of records. Data were presented by medical scientists from the participating countries. After thorough and threadbare discussions, a unanimous statement was issued on the concluding day (Tables 5 and 6). These have been widely published in several international journals. Both ADA and WHO classification committees have taken these into consideration and partly adopted the recommendations.

Table 5. Malnutrition Modulated Diabetes Mellitus

- There is a clinical syndrome of diabetes mellitus that occurs in developing countries in young individuals with a history of, or signs of malourishment
- The physical characteristics of the patients with this syndrome at presentation and the metabolic course of the treated disease differ from those that are usual among patients with NIDDM in developed countries. These patients do not have FCPD
- The patients require insulin for glycemic control but are not ketosis prone

Essentially there was unambiguous and unreserved recognition of the two variants PDDM and FCPD, that were different from each other. Regarding PDDM, it was felt that evidences were not adequate to accept that protein deficiency was the sole cause, while the role of overall malnutrition was obvious in modifying the clinical behaviour and early onset. The term Malnutrition Modulated Diabetes Mellitus (MMDM) was therefore, unanimously adopted as more suitable for this clinical form of diabetes.

Table 6. Evidence summary: fibrocalculous pancreatic diabetes

1. Fibrocalculous Pancreatic Diabetes (FCPD) is a form of diabetes seen mainly in tropical and developing countries.
2. FCPD is due to chronic calculus pancreatopathy, not due to chronic alcoholism or other recognized causes of pancreatitis such as hyperparathyroidism.
3. It is usually seen in young and malnourished individuals but also occurs in others.
4. Diabetes and pancreatic calculi and/or ductal dilation are essential features. Recurrent abdominal pain and steatorrhoea are other important features but absence of these does not preclude the diagnosis.
5. Hyperglycemia may vary from severe to mild; ketosis is uncommon.
6. Pancreatic calculi are usually large, multiple and intraductal. Marked ductal dilatation and fibrosis are usual; inflammatory changes are uncommon.
7. Abnormal exocrine pancreatic function is invariably present but is often demonstrable only following investigations.
8. FCPD is associated with an increased risk of pancreatic carcinoma.
9. Management of FPCD includes treatment of diabetes, oral pancreatic enzyme replacement and relief of pain. Surgery may be required for severe intractable pain and for other indications.
10. The etiology of FCPD is uncertain. The roles of nutrition (including intrauterine nutrition), other environmental exposures and genetic factors need further investigation.

Further, it was felt that malnutrition, as a factor, could not be paramount in the genesis of FCPD. Moreover, as diabetes occurred obviously in association with pancreatic ductal and acinar disorder, it was to be classified with other secondary forms of diabetes. These recommendations have been adopted by both ADA and WHO committees..

Data from Orissa

Incidence

As presented in Table 7, MMDM constituted 5.2% of all patients of diabetes seen at our hospital at Cuttack compared to FCPD, which accounted for 2.2 and IDDM for 0.9%. Among young patients (9% of total) around half were noted to have MMDM. Proportion of the above 3 categories of cases and of NIDDM in the young seen in the hospitals and comparative incidence among patients seen in private clinics[6] at Cuttack are presented in Fig 5. Patients with so called MRDM are much more often seen in charitable hospitals compared to private clinics obviously for economic reasons.

Table 7. Comparison of two types of youth onset diabetes

	MMDM	FCPD
Incidence among diabetics		
All ages	5.2%	2.2%
Upto 30 years	52.5%	22.4%
Age at onset	10-30	10-40
Male/female ratio	2.5:1	3:1

Relative proportion of patients with MMDM, FCPD, Type 1 and Type 2 diabetes among cases with onset by 30 years as documented at Berhampur (Orissa), Cuttack (Orissa) and Dhaka (Bangladesh)[6] is illustrated in Fig. 6. Geographic distribution of FCPD in Orissa is presented in Fig. 7.

Complications

A variety of pyogenic and fungal infections of skin, mucous membrane and tissues, as well as pulmonary tuberculosis occur frequently in patients with MMDM; and relatively less commonly in patients with FCPD (Table 8). Features of neuropathy (reversible, distal symmetrical, sensory polyneuropathy) are extremely common in undernourished patients with MMDM (77%) as well as in FCPD (40%). These complications are noted at first observation, or early during the course of treatment. Macrovascular complications are rare, except peripheral vascular disease, which is elicited by bedside clinical tests rather than by symptoms such as claudication or dry gangrene.

Table 8. Incidence of complications (%)

	PDDM (MMDM)	FCPD
Infection	38	10
Macrovascular		
Coronary artery disease	-	-
Cerebrovascular disease	-	-
Peripheral vascular disease	10	20
Microvascular		
Nephropathy	10.2	10.4
Retinopathy	21.4	14.4
Neuropathy	77	40

Immunogenetics

Genetics and immunological studies of patients with MMDM (71) and FCPD (47) as well as type 1 (74) and type 2 (216) diabetes along with 122 controls from Cuttack have been carried out at the laboratory of C.B. Sanjeevi of the Karolinska Institute, Stockholm, Sweden. Either

GAD or 1A-2 Ab test was positive in around 25% of patients with MMDM. The association was significantly higher than controls while it was much lower relative to type 1 and similar to that in patients with type 2 diabetes.

There are differences in the incidence of genetic markers of MMDM and type 1 diabetes. In antibody positive patients HLA DR_3-DQ_2 set up was common but not DR_4-DQ_8. In the larger fraction of patients who were Ab negative there was increased association of MMDM with DR_7-DQ_9. Further, MMDM was positively associated with allele 9 of MIC-A in the class 1 region and negatively so with allele 5 only. These findings suggest that MMDM is immunogenetically different from type 1 diabetes in several respects[21,22].

Incidence of antibody positivity among patients with FCPD was not different from those in controls. There was no HLA identity either except that some positive association was observed with DQ_9.

Epilogue

There has been a decline in the number of new cases of MMDM and FCPD reporting to the diabetes clinics at Cuttack in the course of the last 5-6 years. Incidence of cases of Tropical Calcific Pancreatitis observed at the Gastroenterology Section is also on the decline. This may be due to improvement in the nutritional status of the rural poor particularly in the endemic coastal districts of Orissa.

Fig. 1 Typical patients with MMDM

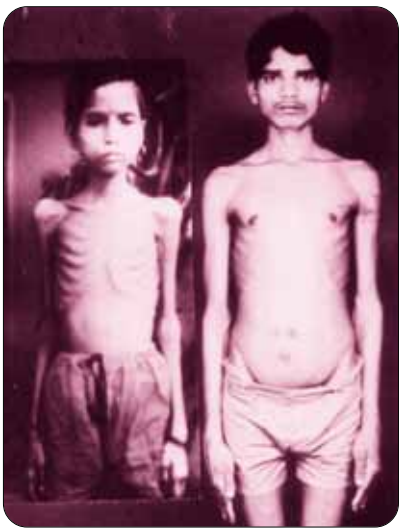


Fig. 2 Patients of FCPD. Abdominal scar of pancreaticolithotomy in one patient

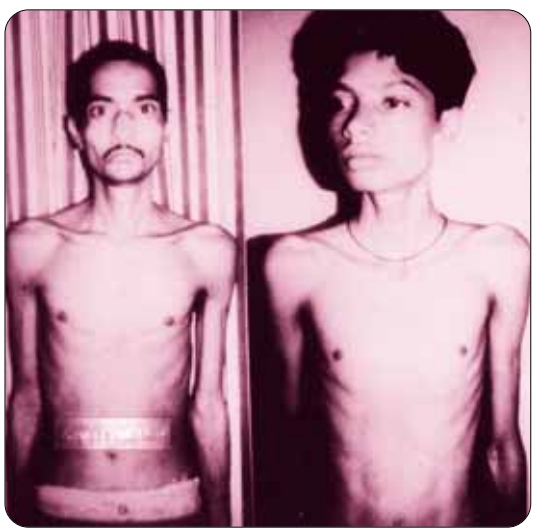


Fig. 3 Basal C-peptide levels at admission and after ~10 years of follow up

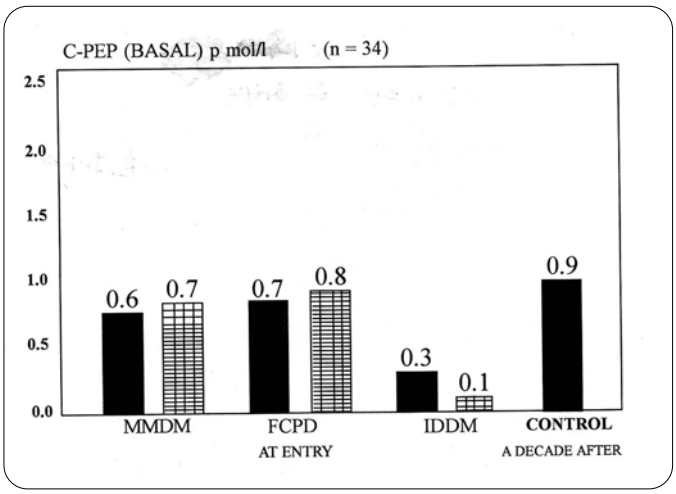


Fig. 4 Hypothesis of the pathogenetic mechanism of MMDM

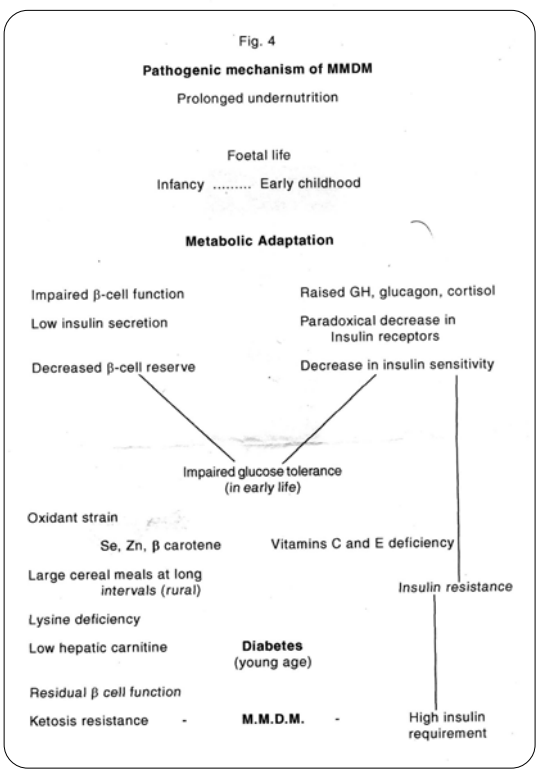


Fig. 5 Incidence of clinical types of diabetes among young patients in Hospital and Domiciliary practice

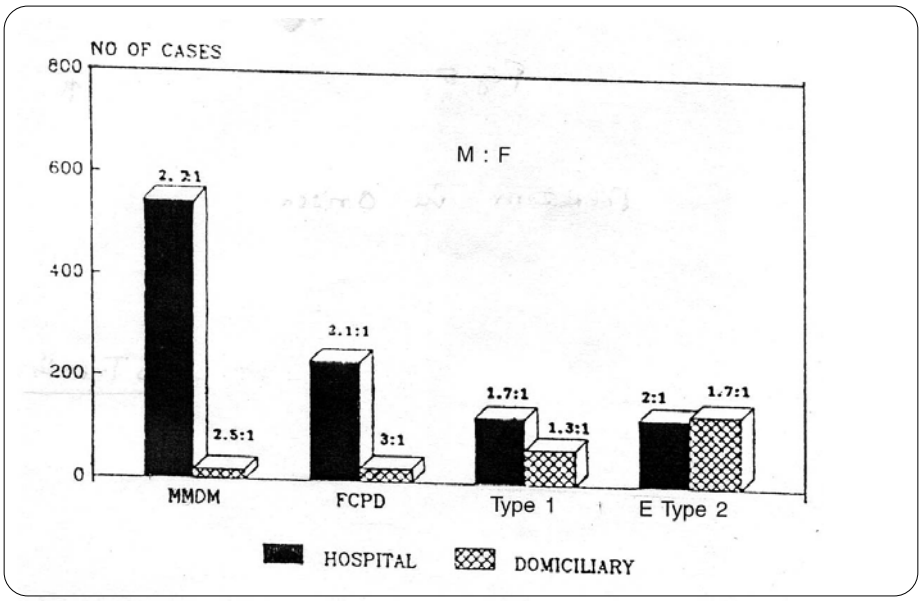


Fig. 6 Hospital based incidence of clinical types of diabetes among young patients observed at Berhampur, Cuttack and Dhaka

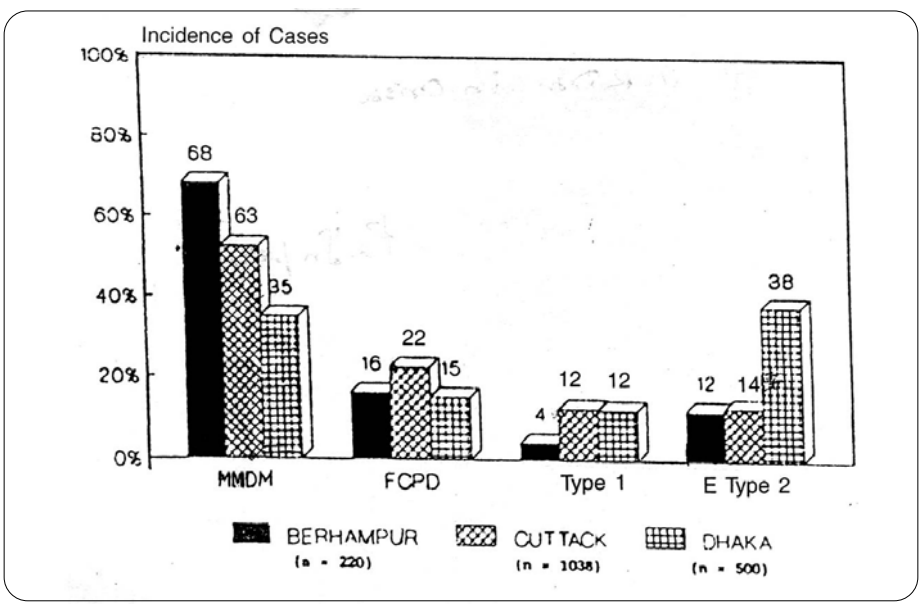
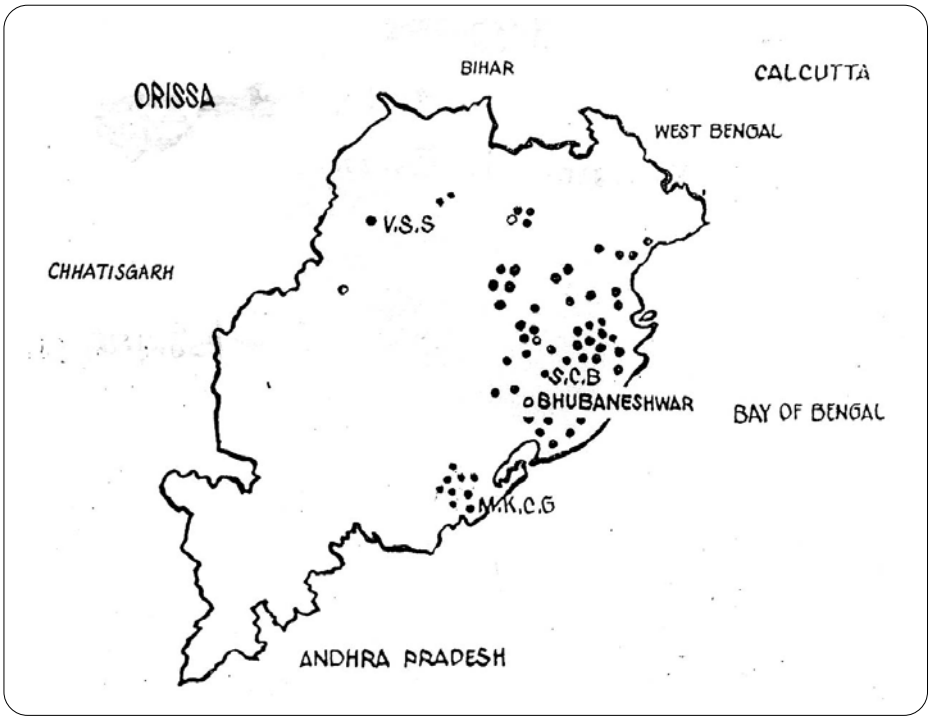


Fig. 7 Map depicting the geographic distribution of FCPD in Orissa



References

1. Hugh-Jones P. Diabetes in Jamaica Lancet 1955; I: 891-97.
2. Geevarghese PJ, Pillei VK, Joseph MP and Pichumani CS. The diagnosis of pancreatogenous diabetes mellitus. J assoc Phys India 1962; 10: 173-80
3. Bose KC. Diabetes mellitus and its prevention. Ind Med Gaz 1995; 30: 135-44
4. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Geogr Med 1959; 11: 70-74
5. Shaper AG. Chronic pancreatic disease and protein malnutrition. Lancet 1960; I: 1223-24
6. Tripathy BB, Samal KC. Protein Deficient Diabetes Mellitus (PDDM) in India. Int J Diab Dev Count 1993; 13: 3-13
7. Heard CRC, Turner MR. Glucose tolerance and related factors in dogs fed diet of suboptimal protein valve. Diabetes 1967; 16: 96-107
8. Baig A, Edozien JC. Carbohydrate metabolism in Kwashiorkor. Lancet 1965; ii: 62-65
9. Khardori R, Bajaj JS, Deo MG and Bansal DD. Insulin secretion and carbohydrate metabolism in experimental protein malnutrition. Endocrinol Invest 1980; 3: 273-78
10. Neel JV. Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress". Amj Hum Genet 1962; 14: 353-62
11. Hales CN and Barker DJP. Type 2 (non-insulin dependent) diabetes: The thrifty phenotype hypothesis. Diabetologia 1992; 35: 595-601
12. Bajaj JS, Rao S, Subarao G, Subarao J and Khardori R. A mathematical model for insulin kinetics and its application to protein deficient (malnutrition-related) diabetes mellitus (PDDM). J Theor Biol 1987; 126: 491-593
13. Nagalotimath SJ, in Hoet JJ, Tripathy BB. International workshop on types of diabetes peculiar to the tropics – Cuttack, India, 1995
14. Geevarghese PJ, Pancreatic Diabetes. Popular Prakashan, Bombay, 1968
15. National Diabetes Data Group (NDDG). Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28: 1039-57
16. Expert committee on diabetes mellitus, second report. WHO Technical Report Series 646, WHO, Geneva 1980
17. WHO Study Group on diabetes mellitus, WHO Technical Report Series 727, WHO, Geneva, 1985

18. Mohan V, Ramachandran A and Viswanathan M. in the Diabetes Annual 4, Alberti KGMM and Krall LP, eds. Elsevier, Amsterdam, 1988; pp 46-55

19. Tripathy BB, Samal KC. Overview and consensus statement on diabetes in tropical areas. Diab Metabol Rev 1997; 13: 63-76

20. Mohan V, Sadhasivaya J, Nagalotimath SJ, Yajnik CS ant Tripathy BB. Fibrocalculous Pancreatic Diabetes. Diab Metabol Rev 1998; 14: 153-70

21. Sanjeevi CB, Kanungo A, Shtauvere A, Samal KC, Tripathy BB. Association of HLA Class II alleles with different subgroups of diabetes mellitus in Eastern India identify different associations with IDDM and malnutrition-related diabetes. Tissue Antigens 1999; 54: 83-87

22. Sanjeevi CB, Kanungo A, Samal KC. Immunogenetic studies on malnutrition modulated diabetes mellitus. Ann NY Acad Sci 2002; 958: 144-47

Chapter 18

Vascular complications in fibrocalculous pancreatic diabetes

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Summary

Fibrocalculous pancreatic diabetes (FCPD) is distinctive because of its predilection towards younger subjects, occurrence in the tropics, rapid progression of exocrine damage and predisposition to malignancy. Do the endocrine-related i.e. diabetes-linked complications too occur and progress rapidly as well? This article will focus on the link between FCPD and diabetes-related vascular complications. Increasingly, evidence seems to suggest that microvascular complications, which are specific to the diabetic milieu, are as common in FCPD as compared to other subtypes of diabetes. Macrovascular complications are reportedly rare in these subjects, as they are younger, leaner, and have lower cholesterol levels. However, macrovascular complications are being increasingly reported in FCPD subjects from India. In this article, we focus on the link between FCPD and vascular complications, and also present the data from our center.

Introduction

Earlier, the genesis of fibrocalculous pancreatic diabetes (FCPD) had been attributed to malnutrition.[1] Today, it is increasingly being recognized that FCPD is a form of secondary diabetes.[2] This paradigm shift has occurred because of the recognition that the etiological links between malnutrition and diabetes are at best tenuous, i.e. pancreatic damage is the reason for malnutrition, and not vice versa. This has led the American Diabetes Association to characterize FCPD as a secondary form of diabetes.[3]

Accepting this view, it becomes logical to assume that the hyperglycemic milieu in fibrocalculous pancreatic diabetes is essentially dependent on the extent and duration of pancreatic beta cell damage.[4] A corollary of this view would be that diabetes-related vascular complications would occur as commonly in FCPD as in type 1 or type 2 diabetes, as it has been well proven that diabetic-vascular complications are inextricably linked to the duration and severity of hyperglycemia.[5,6] Presently, the bulk of available evidence on FCPD supports this view, however there are some caveats.

Microvascular disease

The microvascular complications, i.e. neuropathy, nephropathy and retinopathy are relatively diabetes-specific. Unlike *macrovascular* complications like coronary artery disease, which can also occur in non-diabetics, the unique pattern of microvascular damage is not seen in non-diabetic individuals. Studies on fibrocalculous pancreatic diabetes have shown that *microvascular* complications do occur in them as commonly as in other subtypes of diabetes.[7]

As early as in 1985, it was reported that sight-threatening retinopathy could occur in FCPD.[8] In this study of 40 patients from South India with FCPD, it was reported that 13 subjects had retinopathy. In addition to background retinopathy, the authors reported the occurrence of macular edema and proliferative retinopathy requiring laser therapy. Thus in this study, diabetic retinopathy was present in about one third of subjects with FCPD. Subsequently, retinopathy has been reported to be about 30% in FCPD.[9]

The prevalence of overt nephropathy among FCPD subjects is about 10%.[9] However, microalbuminuria could be more common; in a study on African subjects with pancreatic diabetes about 33% had microalbuminuria.[10] Notably, in the only published study on the long-term survival of subjects with FCPD, diabetic nephropathy was the leading cause of death.[11]

As far as neuropathy is concerned, the prevalence is reported to be about 44%, making it a common microvascular complication of diabetes.[12] Most subjects with fibrocalculous pancreatic diabetes also have malabsorption due to pancreatic enzyme deficiencies. Therefore, it is possible that nutritional deficiencies, and even the additive effects of moderate alcohol consumption might increase the occurrence of neuropathy. In contrast to other diabetic complications, neuropathy seems to correlate very well with the duration of diabetes, and in one study, autonomic neuropathy was found in over 60% of subjects with FCPD after 16 years of diabetes.[13]

Overall, these data seems to suggest that microvascular diseases are as common in FCPD as in other subtypes of diabetes.[14] It is important to

address the issue of whether vascular complications are as common in FCPD as compared to other subtypes of diabetes. In a recent study, FCPD was compared to other subtypes of diabetes in the young.[12] As compared to age-matched subjects with type 2 diabetes, malnutrition modulated diabetes, and type 1 diabetes, subjects with FCPD had a similar prevalence of microvascular disease. It was reported that the prevalence of neuropathy was higher in subjects with fibrocalculous pancreatic diabetes as compared to other subtypes of diabetes. This study showed the prevalence of microvascular complications relatively early on after diagnosis. At our center too, microvascular complications are seen in about one-fourth of subjects with FCPD (see below). Taken together, these studies confirm the need to screen for microvascular complications in these subjects.

Macrovascular disease

The issue of macrovascular disease in fibrocalculous pancreatic diabetes is quite fascinating because this gives an insight into the changing profile of FCPD. To begin with, macrovascular complications of diabetes are rare in FCPD. This has been attributed to three factors: the younger age of the subjects, lower body mass index and lower cholesterol levels.[14] However, reports of macrovascular complications have become more frequent.[15] Stroke, peripheral vessel disease (PVD), coronary artery disease (CAD), and hypertension have all been reported in FCPD.[16-18] It has been reported that about 4.7% of subjects with FCPD have peripheral vessel disease, and about 5% have coronary artery disease.[9]

While the association between FCPD and macrovascular disease is now only in the realm of anecdotal case reports, there are several interesting facets to this issue. It is tempting to speculate that this changing profile is in some way linked to the increasing occurrence of insulin resistance syndrome (including type 2 diabetes and coronary artery disease) in the Indian subcontinent. In other words, could the predisposition to macrovascular disease be linked to the co-existence of type 2 diabetes in these subjects? This is an interesting area for further study, but it is difficult to design a trial to address this issue, obviously because of the difficulty in conclusively proving the co-existence of type 2 diabetes and FCPD in these subjects.

Could the macrovascular disease be in some way linked to insulin resistance? Using parameters of insulin resistance, a recent study has investigated insulin sensitivity in FCPD and compared the same with other age-matched subtypes of diabetes. [12] Four groups of young diabetic subjects were studied: FCPD, type 2 diabetes, malnutrition modulated diabetes, and type 1 diabetes. The area under insulin curve (AUC) was measured by doing a glucose tolerance test, and checking serum insulin levels every 30 minutes for two hours. In this study, FCPD subjects had higher insulin levels as compared to subjects with type 1 diabetes as well as those with malnutrition modulated diabetes mellitus.[12] Among young diabetics, only type 2 diabetics had higher AUC values. In addition, in a second analysis of the same group, FCPD subjects had higher values of insulin resistance as measured by the homeostasis assessment model.[18]

The intravenous insulin infusion test showed that over 60% of these FCPD subjects were insulin resistant.[12] The study concluded that subjects with FCPD had significant values of insulin resistance when compared with type 1 diabetes as well as malnutrition-modulated diabetes .As the extent of hyperglycemia was similar in these groups, the defect in insulin action cannot be attributed to glucose toxicity, i.e. a toxic effect of hyperglycemia on the insulin action pathways. However, this observation is somewhat intriguing and could well be a chance finding, considering that other reports have shown that the amount of insulin required in FCPD is only about 40 units per day.[14,18]

Interestingly, it has also been reported that young subjects with FCPD had a significantly higher triglyceride levels (when compared with age-matched type 1 diabetics, malnutrition-modulated diabetes as well as controls).[12] Hypertriglyceridemia is associated with both pancreatic damage and insulin resistance. It would also be useful studying the effects of oxidant stress in FCPD, as oxidant stress has been linked to the genesis of FCPD as well as with the insulin resistance syndrome.[18-21]

Vascular complications in FCPD: our experience

The audit from the pancreas clinic at the Amrita Institute of Medical Sciences also shows a similar profile when compared with other studies

regarding the prevalence of microvascular and macrovascular complications. A total of 48 cases of fibrocalculous pancreatic diabetes, seen over a period of one year, underwent evaluation for diabetic complications, glycemic control and lipid profiles.

The mean age at onset of FCPD was 33.4 yrs. The mean duration of diabetes at presentation was 8.8 years. Even though the majority of subjects (28/48) had onset of DM after pancreatitis, a significant number (13/48) had DM preceding CCP. Most of the patients were either non-obese or lean and the mean BMI was 18.8 kg/m^2.

Glycemic control as assessed by the mean HBA1c was fair (8.2 %), but the mean fasting and postprandial plasma glucose levels were high (159mg/dl and 306mg/dl respectively) at the time of initial visit .We postulate that these uncontrolled blood glucose values (given the concomitant HbA1c value) could be related to repeated episodes of hypoglycemia and hyperglycemia, thus leading to brittle diabetes in the FCPD patients. The lipid profiles also showed a favorable trend with a mean triglyceride value of 106 mg/dl, a mean LDL of 112.9mg /dl and a mean HDL of 48 mg/dl. In general, subjects with FCPD are reported to have low cholesterol levels; the relatively high LDL levels in our series are probably linked to suboptimal glucose control.

About one fourth (23%; 11/48) of our subjects had microalbuminuria, diagnosed when the value for urine albumin-creatinine ratio was more than 30 ug/mg. A similar proportion i.e. 27%(13/48) had neuropathy as diagnosed by neuropathic symptoms along with abnormal biothesiometry.

Among the FCPD subjects,15 %(7/48) had retinopathy on dilated fundus examination Coronary artery disease as evidenced by history of angina or myocardial infarction and/or ECG changes was present in only 4.2%(2/48) and peripheral occlusive vascular disease detected by ankle brachial index and confirmed by doppler evaluation was seen in only 2.1%(1/48)cases. To summarize, our experience is in keeping with that from other centers in the country, with about one fourth of subjects having microvascular complications. The prevalence of macrovascular disease was low in our series.

Conclusions

Microvascular complications are as common in FCPD as compared with other subtypes of diabetes. Macrovascular disease, particularly coronary artery disease is rare. However, there are several reports of macrovascular complications in FCPD, and the reasons for them are an interesting area for future research.

References

1. World Health Organization. Diabetes Mellitus: Report of a WHO Study Group. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727).
2. Consensus statement. International workshop on types of diabetes peculiar to the tropics, 17–19, October 1995, Cuttack, India. Acta Diabetologica Latina 1996; 33:62-4.
3. American Diabetes Association: clinical practice recommendations 2000. Diabetes Care. 2000;23 Suppl 1:S1-116.
4. Mohan V. Diabetes in the tropics. In : Alberti KGMM, Zimmet P, Defronzo RA, Keen H. eds. International Text Book of Diabetes, 2nd Edition. Chichester : John Wiley and Sons; 1997: 171-88
5. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986.
6. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and the risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837-53
7. Mohan V, Premalatha G, Pitchumoni CS. Tropical chronic pancreatitis: an update. J Clin Gastroenterol. 2003;36:337-46.
8. Mohan R, Rajendran B, Mohan V, Ramachandran A, Viswanathan M, Kohner EM. Retinopathy in tropical pancreatic diabetes. Arch Ophthalmol. 1985;103:1487-9.
9. Kanta Barman K, Padmanabhan M, Premalatha G, Deepa R, Rema M, Mohan V. Prevalence of diabetic complications in fibrocalculous pancreatic diabetic patients and type 2 diabetic patients: a cross-sectional comparative study. J Diabetes Complications. 2004;18:264-70.
10. Levitt NS, Adams G, Salmon J, Marks IN, Musson G, Swanepoel C, Levy M, Byrne MJ. The prevalence and severity of microvascular complications in pancreatic diabetes and IDDM. Diabetes Care. 1995;18:971-4.
11. Mohan V, Premalatha G, Padma A, Chari ST, Pitchumoni CS. Fibrocalculous pancreatic diabetes. Long-term survival analysis. Diabetes Care. 1996;19:1274-8.

12. Jyotsna VP, Singh SK, Gopal D, Unnikrishnan AG, Agrawal NK, Singh SK, Dixit VK, Agrawal AK, Agrawal JK. Clinical and biochemical profiles of young diabetics in North-Eastern India. J Assoc Physicians India. 2002 ;50:1130-4.

13. Mohan V, Sastry NG, Premalatha G. Autonomic dysfunction in non-insulin-dependent diabetes mellitus and fibrocalculous pancreatic diabetes in south India. Diabet Med.1996 Dec;13(12):1038-43.

14. Barman KK, Premalatha G, Mohan V. Tropical Chronic Pancreatitis Postgrad Med J. 2003 ;79:606-15.

15. Chattopadhyay PS, Mukhopadhyay J, Chattopadhyay R, et al. Macrovascular disease is not that uncommon in fibrocalculous pancreatic diabetes (FCPD). Diabetes Care 1994;17:462-3.

16. Mohan V, Ramachandran A, Viswanathan M. Two case reports of macrovascular complications in fibrocalculous pancreatic diabetes. Acta Diabetol 1989;26:345-9.

17. Sastry NG, Mohan V. Hemiplegia in a patient with fibrocalculous pancreatic diabetes. J Assoc Physicians India 2000;48:1129

18. Unnikrishanan AG, Sahay RK, Bhadada SK, Agrawal NK, Singh SK, Agrawal JK. Fibrocalculous pancreatic diabetes and macrovascular disease. J Assoc Physicians India. 2001;49:1131-33.

19. Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. J Am Coll Cardiol. 2004 Dec 21;44(12):2293-300.

20. Braganza JM, Schofield D, Snehalatha C, et al. Micronutrient antioxidant status in tropical compared with temperate zone chronic pancreatitis. Scand J Gastroenterol 1993;28:1098-104.

21. Braganza JM, Sherry J, Indira P, et al. Xenobiotics and tropical chronic pancreatitis. Int J Pancreatol 1990:222-45.

Chapter 19

Genetic studies in chronic pancreatitis in India

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Summary

Background Aims : *Mutations in cationic trypsinogen (PRSS1) gene are causally associated with recurrent acute and chronic pancreatitis. We investigated whether mutations in PRSS1 gene are associated with hereditary and non-hereditary pancreatitis. Since a modifier role has been proposed for trypsion inhibitor (SPINK 1) mutations, the role of SPINK1 mutations in these patients was also analyzed.*

Subjects and Methods: *The coding regions of PRSS1 and SPINK1 genes were sequenced in 290 controls and 304 patients, of whom 106 were diagnosed as tropical calcific pancreatitis (TCP), 120 as idiopathic (ICP), 41 as alcoholic (ACP), and 37 as hereditary pancreatitis (HP). Twenty-four unaffected relatives of HP probands were also analyzed and genotype-phenotype correlations and statistical analyzes were performed.*

Results: *No mutations in PRSS1 gene were detected in any of the patients including hereditary pancreatitis, while N34S mutation was observed in SPINK1 gene of majority of HP patients (73%). Similarly, 26.8% of ACP (11 of 41) and 32.8% (39 of 120) of ICP patients and 42.5% (45 of 106) of TCP patients had SPINK1 mutations. N34S mutation was observed in both homozygous as well as heterozygous condition. In comparison, only 2.76% of control population had N34S allele ($P<0.001$). P55S mutation was observed in one patient each of ICP and ACP and 2 TCP patients and 3 normal individuals. Genotype-phenotype correlation did not suggest any significant difference in the age of onset, severity of disease or pancreatic endocrine insufficiency in patients with or without mutated SPINK1 and irrespective of the allelic status of N34S SPINK1. However, FCPD patients had an earlier age of onset but comparable prevalence of SPINK1 mutation as opposed to TCP patients without diabetes mellitus.*

Conclusions: *Irrespective of the etiology, mutations in PRSS1 gene are not associated with CP including hereditary pancreatitis. On the contrary, N34S mutation in SPINK1 gene shows significant correlation in these patients, albeit with variable prevalence in each etiological type. The results suggest a common genetic basis for TCP with additional factors responsible for the variability of phenotype in FCPD and TCP without diabetes mellitus. A comparable phenotype in terms of age of onset, diabetes mellitus and other phenotypic features in patients with or without SPINK1 mutations and N34S homozygotes and heterozygotes suggests that there may still be involvement of other genetic or environmental factors.*

Introduction

Chronic pancreatitis (CP) is a global health care problem with varied etiologies. Alcohol is generally considered as an important risk factor for the development of chronic pancreatitis. However, additional factors like heredity, smoking, anatomical variations and metabolic disorders like hyperlipidemia and hypercalcemia have also been identified. About 20% to 30% of such cases fall in the category of idiopathic chronic pancreatitis (ICP) since the causal factor in them is yet to be known. Although the exact pathogenesis is not clear, autodigestion secondary to aberrant intraductal activation of zymogens by trypsin is a primary common event. Several genetic risk factors for CP have been identified recently.

The genetic basis of CP was first reported in 1996 by familial linkage analysis and confirmed by detection of missense mutations namely R122H and N29I in cationic trypsinogen gene (PRSS1) in hereditary pancreatitis (HP) patients. Subsequent efforts to investigate the presence of HP-associated PRSS1 mutations showed a very low incidence in ICP and complete absence in alcohol related pancreatitis (ACP). Overall, only about 60% cases of HP and less than 20% with a diagnosis of ICP have a mutated PRSS1 gene. The underlying causes of variability in penetrance are not clear, but the observations indicate the involvement of environmental as well as other genetic factors. More recently, N34S mutation of the serine protease inhibitor, Kazal type I (SPINK1), has been reported to be strongly associated with idiopathic and familial pancreatitis. Subsequent studies, however, have reported low prevalence of mutated SPINK1 gene in ICP patients. The role of SPINK1 mutations particularly N34S mutation is a matter of controversy with some suggesting a causal while others advocating a modifier role for this molecule.

Tropical calcific pancreatitis (TCP) is an idiopathic, juvenile, non-alcoholic form of CP widely prevalent in several tropical countries whereas Fibrocalculous pancreatic diabetes (FCPD) is a form of diabetes secondary to TCP. The disease differs from alcoholic pancreatitis by much younger age of onset, pancreatic calcification, a high incidence of insulin dependent but ketosis resistant diabetes mellitus and exceptionally high incidence of pancreatic cancer. We analyzed a large cohort of patients with hereditary and non-hereditary pancreatitis (ICP, ACP and TCP) to

determine if PRSS1 and SPINK1 mutations are associated with CP in India and also to understand their respective roles in the causation of disease. We found no mutations in PRSS1 gene but detected only SPINK1 mutations in all types of pancreatitis patients. We therefore propose genetic basis of CP (irrespective of its etiology) in India to be different to what has been observed in the Western countries. The observations made in this study may have implications in counseling and modification of the predisposition risk by avoiding exposure to possible precipitating factors such as alcohol, smoking and nutrition etc. in India.

Subjects and methods

Selection of patients

The diagnosis of CP was based on at least two separate episodes of abdominal pain and radiological findings of pancreatic calcifications by Computed tomography, Endoscopic ultrasonography and/or pathological findings like pancreatic ductal irregularities and dilatations on Endoscopic retrograde cholangiopancreatography. A detailed questionnaire including the clinical and family history and various investigations was collected from all the patients and their unaffected relatives willing to participate in the study. Clinical history included etiology, type and severity of pain, frequency of attacks, presence or absence of diabetes mellitus, age at onset of symptoms and of diabetes mellitus etc. Exclusion criteria for diagnosis of ICP included the absence of precipitating factors such as alcohol, gallstones, infection, trauma, medications and metabolic disorders, age over 65 years and a positive family history. Alcohol was considered causal in CP patients with a daily intake equivalent to more than 80 g of ethanol for at least two years. A diagnosis of HP was made on the basis of at least two affected first degree relatives or three or more second degree relatives in two or more generations. Patients were categorized as TCP based on the established WHO criteria.

Thus, in total 304 patients (120 ICP, 41 ACP, 106 TCP and 37 HP) and 24 unaffected relatives from HP families participated in the study. 290 healthy volunteers constituted the control population. Blood samples were drawn using EDTA as anticoagulant after collecting written informed consent.

DNA analysis

Genomic DNA was isolated from leucocytes following standard protocols. Since there is no report on genetics of CP in Indian population, PRSS1 and SPINK1 genes were sequenced to screen for the reported as well as for any novel mutations. The primer sequences were selected from the published sequences and nested PCR strategy was used to amplify PRSS1 gene since it is highly homologous with other trypsinogens. Sequencing was done on both the strands using Big dye terminator cycle sequencing ready kit on a DNA Sequencer. 580 control alleles were also sequenced to identify the prevalence of PRSS1 and SPINK1 variants in the general population.

Statistical analysis

All values are presented as median (range, 95% CI). Chi-Square test was used to analyze differences in prevalence of SPINK1 and N34S mutation among ICP, ACP, TCP and HP patients as well as controls. We categorized the study cohort based on presence or absence of N34S SPINK1 mutation and its zygosity. Phenotypic variability in features like age of onset and presence or absence of diabetes mellitus etc. among these groups was analyzed by applying Mann-Whitney U test using SPSS® software. A p value less than 0.05 was considered statistically significant.

Results

Patient details

Our study cohort comprised 37 HP patients from 16 families and 267 patients with non-hereditary pancreatitis (120 ICP, 41 ACP and 106 TCP patients). There were 232 males and 72 females but all ACP patients were exclusively male. Majority of patients presented with pain in the abdomen (91%), while diabetes mellitus was the presenting symptom in the rest. The median age of onset for HP, ICP and TCP patients was comparable at 24.5, 23.5 and 25.0 years respectively, which was significantly lower than 36 yrs for ACP patients ($P<0.001$). However, HP patients reported a longer duration of disease compared to other categories (Table 1).

DNA Analysis

On sequence analysis, none of the patients or controls carried either the common mutations or any novel variant in the coding region of PRSS1 gene. However, two commonly reported neutral polymorphisms 162Asp (GAC>GAT) and 246Asn (AAC>AAT) were observed in majority of patients (88%) as well as in the controls (90%, P>0.05). In comparison, 122 CP patients (40.1%) had at least one SPINK1 mutation. Majority of patients (n=118) carried N34S allele including 38 homozygotes and 80 heterozygotes. (Table 2) N34S mutation was found to be in complete linkage disequilibrium with IVS1-37T>C. P55S was observed in heterozygous state in only 4 patients (1.3%). The previously reported neutral polymorphism –253T>C was identified in heterozygous state in 3.5% of patients and 27.9% of controls. Eight out of 290 healthy controls also carried N34S mutation (2.76%, allele frequency= 0.014) while P55S was observed in only three individuals (1.03%, allele frequency=0.0017). Both mutations were present in heterozygous state and no other previously reported mutations like 2T>C, 41T>C etc. were detected in these patients.

Thirty-eight of 120 ICP patients (31.7%) carried N34S mutation (P<0.0001 vs. controls), of which 7 were homozygous. However, no significant difference in N34S SPINK1 mutation frequency was noted for early onset (35.7%) and late onset form (22.2%, P=0.3872) of ICP. Interestingly, we identified N34S mutation in 10 of 41 ACP patients (24.4%, P<0.0001 vs. controls), which is significantly higher compared to earlier studies reporting frequencies ranging between 5.6-6.0%. All of them were N34S carriers except one P55S heterozygote and one N34S homozygote. Till date, no N34S homozygote has been reported in this group of patients. This individual was a 31-year-old patient with persistent pain since the age of 20 yrs and diabetes for 2 years and very low alcohol intake for last 5 years. Although the diagnosis of ACP is based on a history of excessive alcohol intake in the background of recurrent attacks of AP, the amount of alcohol intake has been reported to vary from 25 g/day to more than 80 g/day for 5 years. Of 16 families matching the criteria of HP, 12 (75%) carried N34S SPINK1 mutation. 73% of HP patients (P<0.0001 vs. controls) were positive for N34S mutation and included 7 homozygotes. Interestingly, all N34S

homozygotes in this group were diabetic with the age of onset between 5 and 12 years. Of 24 unaffected relatives, 6 (25%) carried N34S SPINK1 mutation. The only homozygote was a 23-year-old individual without pancreatitis or diabetes mellitus, although his heterozygous parents had the disease.

SPINK1 mutations were also detected in 45 out of 106 (42.5%) TCP patients analyzed. Of 43 patients with N34S mutation, 10 were homozygous, 32 heterozygous and 1 compound heterozygote with P55S (Fig 1a). We detected SPINK1 mutations in both FCPD patients and TCP patients without diabetes mellitus in comparable frequency. A novel G to T transversion at 215 bp upstream in the SPINK1 promoter region (-215G>T) was also identified in 3 patients, who interestingly also carried an N34S allele, suggesting a compound heterozygote status (Fig 1b).

Genotype-phenotype correlation

We categorized the study cohort according to etiology and then compared the SPINK1 N34S positive and negative patients in each category as a function of various phenotypic markers (Table 3). The median age of onset and presentation for FCPD patients was 35.0 and 44.0 yrs respectively, which is significantly higher than that of TCP patients without diabetes mellitus 21.0 ($P<0.004$) and 26.0 yrs ($P<0.001$). The age of onset of symptoms was lower in the group with N34S SPINK1 compared to the group carrying wild type SPINK1 in each category but did not reach statistical significance except in HP patients ($P=0.045$). Analysis of N34S carrier frequency after categorizing our study cohort into groups by age showed interesting results. The <20 yrs group had a carrier frequency of 52.8% (28 of 53) which is significantly higher than that of 24.8% (36 of 145) in the 20-65 year-old group ($P<0.016$). Interestingly, majority of homozygotes (14 of 15) had CP before the age of 20 years. The only homozygote in the older group was a 54-year-old patient with mild disease and diabetes for 6 years. An increased contribution of environmental factors in the latter group may have contributed to this significant difference.

Diabetes mellitus as a feature of pancreatic endocrine insufficiency was equally prevalent in both groups and so were other parameters of disease severity, like pain, pseudocysts, pancreatic ductal abnormalities etc. (Table 3). A comparison of SPINK1 mutation frequency in FCPD patients and TCP patients without diabetes showed similar trends suggesting that neither these mutations nor their status is directly related to the presentation of diabetes mellitus (Table 4). Prevalence of N34S SPINK1 mutation (43.1%) in patients with diabetes was similar in patients without diabetes (37.9%) (Table 4). Relatively more N34S homozygotes were observed in patients with diabetes (38.7%) than the group without diabetes mellitus (14.7%). This may be due to additional genetic or environmental factors especially in the HP cohort since the prevalence of N34S mutation was comparable in both the groups. However, association between N34S and diabetes mellitus did not reach statistical significance in all categories of patients.

Data from HP families showed a variable genotype-phenotype association in individual families. In one of the families, the proband was a 40-year-old lady with pancreatitis at 21 and diabetes at 23 yrs (Fig 2). She was detected to be homozygous for N34S SPINK1, which was inherited from her obligate heterozygous healthy parents. Her father was diabetic for last 30 years but of her two obligate N34S heterozygote sons, the younger has both pancreatitis and diabetes for last 5 years, while the elder one is healthy. Three of her brothers were positive for N34S and had diabetes without evidence of pancreatitis. In another family, the proband was an 18-year-old N34S heterozygote, inherited from his heterozygous father who also had early onset of the disease. However, his elder brother and paternal grandmother are healthy despite being heterozygous for N34S SPINK1, whereas two aunts with N34S/WT have severe pancreatitis with diabetes and another heterozygote aunt is only diabetic.

Discussion

Chronic pancreatitis is a heterogeneous disease and its genetic basis in India has not been investigated. We analyzed 304 patients with hereditary and non-hereditary pancreatitis with the major objective of understanding the respective roles of PRSS1 and SPINK1 mutations in

its causation. In the present study, except two previously reported cSNPs, no PRSS1 mutation could be identified in any patient as well as in control individuals. Absence of PRSS1 mutations in HP and ICP patients is intriguing since such mutations have been reported in upto 60% of HP and about 20% of ICP patients. We describe absence of PRSS1 mutations in Indian patients with CP of different etiologies for the first time. This may most likely be related to their genetic makeup since no other study from abroad has reported absence of PRSS1 mutation in HP as well as non-hereditary CP patients. However, interaction with other factors like environmental, nutritional may also play an important role. These results strongly suggest that irrespective of its etiology, established mutations in PRSS1 are not a common cause of CP in the Indian population.

However, SPINK1 mutations were found to be strongly associated with all types of chronic pancreatitis. Most patients with SPINK1 variation had N34S mutation and the prevalence was significantly higher in HP compared to ICP, ACP and TCP ($P<0.001$). The presence of N34S SPINK1 mutation in majority of HP patients is particularly interesting since PRSS1 mutations are lacking in these patients. N34S SPINK1 prevalence (2.76%) in controls is much higher than 1.5% in the French, 1.58% from USA and 0.36% from Germany but much lower than 4% in control population from Liverpool. Therefore, distribution of N34S allele among various populations might be more variable than originally assumed. The observed prevalence of mutated SPINK1 in ICP patients (32.5%) is significantly higher than earlier reports varying from 6.4-21.0% in other studies. A stronger genetic basis has recently been suggested for early-onset ICP than the late-onset ICP but we didn't find any significant association for N34S SPINK1 prevalence, although majority of patients in the older group (12 of 36) presented with diabetes as compared to only 7 of 84 early-onset patients ($P=0.0103$). The higher age of onset for HP patients (24.5 yrs) in our study compared to majority of studies conducted abroad may be due to the presence of N34S SPINK1 mutation, which are hypothesized to perform a modifier role in comparison to the causal role played by PRSS1 mutations in the Western HP patients. A highly significant prevalence of SPINK1 mutations in our cohort of ACP patients suggests an important role for this genetic variant in our population. Decreased trypsin inhibitor to trypsinogen levels has been reported in the pancreatic juice of alcoholics compared with controls

without alcoholism. Alcohol might also affect SPINK1 regulation during the complex inflammatory processes in human alcoholic pancreatitis. Earlier studies have shown that in comparison with white patients, black patients are 2-3 times more likely to be hospitalized for CP than alcoholic cirrhosis. Thus, alcoholics in India may be more susceptible to CP due to a combination of factors like genetic makeup, racial difference in diet, type or quantity of alcohol or smoking etc. Although, the present knowledge suggests that ACP patients are likely to have higher interaction with the environmental factors in comparison to other types of chronic pancreatitis, there is a strong genetic basis for ACP patients in India. Since, SPINK1 mutations appear to predispose humans to an earlier age of onset, they may have an impact on the phenotypic presentation of ACP.

The exact relationship between the phenotype of FCPD and TCP is still not clear, although there is an overlap in their phenotypes. In our study cohort of 106 TCP patients, 30 were FCPD patients while remaining 76 were without diabetes at the time of presentation. Comparison of the age of onset shows that FCPD patients had a late age of onset with a difference of more than a decade (21 yrs vs. 35 yrs). It has also been shown that the patients with TCP are younger than the FCPD patients and majority of them have an abnormal Glucose tolerance test. This strongly suggests that FCPD may be gradually evolving diabetes in the background of TCP. Our study confirms the causal role of N34S mutation in SPINK1 gene in pancreatitis and simultaneously establishes the role of mutated inhibitor in the pathogenesis of TCP. These contradict the earlier observations by Rossi et al suggesting a genetic basis for FCPD only and proposing a clinical distinction within TCP with respect to presence or absence of diabetes mellitus. However, their limited sample size (8 FCPD and 4 TCP patients) raises serious concern about the validity of such a conclusion. Our results suggest a common genetic basis for TCP with additional genetic/environmental factors responsible for the variability of phenotype in TCP and FCPD.

The cohort in this study represents the conglomeration of CP patients usually seen in routine clinical practice in developing countries like India. Such high frequency of SPINK1 gene mutations in the background of complete absence of mutated PRSS1 gene is interesting. Till date, no

study has reported concurrence of mutated PRSS1 with SPINK1 suggesting that both the mutations work through different and independent mechanisms. However, this pancreatic protease-protease inhibitor system is very important, considering the physiological interaction between them in combating the prematurely activated trypsinogen inside the pancreas. Intrapancreatic levels of trypsin are expected to be elevated if mutations in the inhibitor molecule lead to loss of its inhibitory capacity. However, it is difficult to explain the phenotype of pancreatitis in the presence of a normal trypsin when the intact R122 autolysis "self-destruct" mechanism can take care of the prematurely activated trypsin molecule. This suggests impairment of other protective mechanisms involved in combating the prematurely activated trypsin molecule inside the pancreas. The exact mechanism is still not clear and it remains to be proven how, the prematurely activated trypsin is sustained inside the pancreatic acini and may cause a low-grade inflammation and disease. SPINK1 mutations have been proposed to significantly lower the threshold for pancreatitis from other factors. It is hypothesized that mutated inhibitor, with N34S mutation, may have functional consequences probably due to alteration of the protein structure.

The present state of research on the role of N34S SPINK1 is confusing with both causal as well as modifier role. A recent study supports the significance of SPINK1 mutations based on disappearance of pancreas in the homozygous knockout mice of SPINK1, although heterozygous mice showed no alteration in pancreatic tissue. We did not observe any significant difference in the phenotype between SPINK1 mutation positive and mutation negative groups as well as between SPINK1 N34S heterozygotes and homozygotes. Although, the association between N34S and diabetes mellitus was not statistically significant in all the categories of patients, N34S homozygosity was positively associated with diabetes mellitus. This suggests that N34S SPINK1 mutation may be involved in only modifying the phenotype. Several studies have argued about SPINK1 mutations as autosomal recessive or autosomal dominant. Our results may suggest autosomal dominant mode of inheritance with a low level of penetrance. At the same time, autosomal recessive model is also suggested by the high prevalence of N34S homozygotes (7.6%) in patients. Despite a significantly strong

association of N34S with HP, analysis of HP families in our study shows variable inheritance pattern and association with the phenotype. This phenomenon of genetic heterogeneity is a characteristic of complex diseases with an important role of environment. Hence, it may be logical to suggest that the presence of a second mutation, either in the same gene or other genes in association with environmental factors is required to express the disease phenotype.

In conclusion, we demonstrated for the first time, the association of mutated pancreatic secretory trypsin inhibitor with tropical calcific pancreatitis, irrespective of the absence or presence of diabetes mellitus (FCPD). We also showed that N34S mutation in SPINK1 gene is strongly associated with all types of chronic pancreatitis, although the penetrance is quite variable. But mutations in cationic trypsinogen gene are not the important causes of chronic pancreatitis in Indian population. The presence of SPINK1 mutations in both FCPD and TCP patients without diabetes mellitus suggests a common genetic basis for tropical calcific pancreatitis. However, different genetic/environmental factors may be involved to account for phenotypic variability in TCP patients. Till date, N34S SPINK1 mutation is the only factor imparting a genetic basis to chronic pancreatitis in Indian patients. This may have implications in presymptomatic genetic testing, however, analysis of more such patients may validate such a conclusion.

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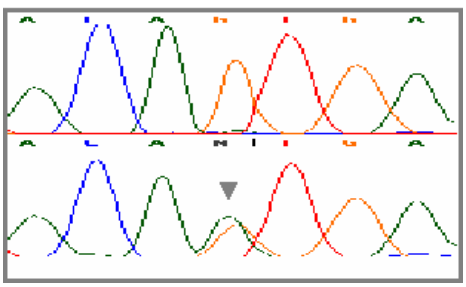
Legends to figures

Figure 1

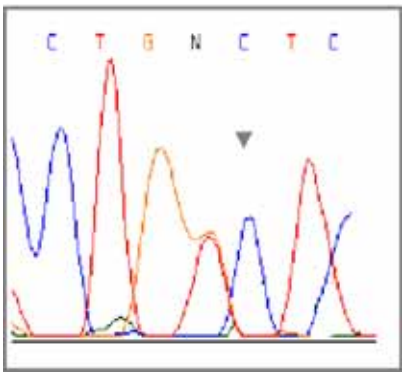
1a

N34



1b

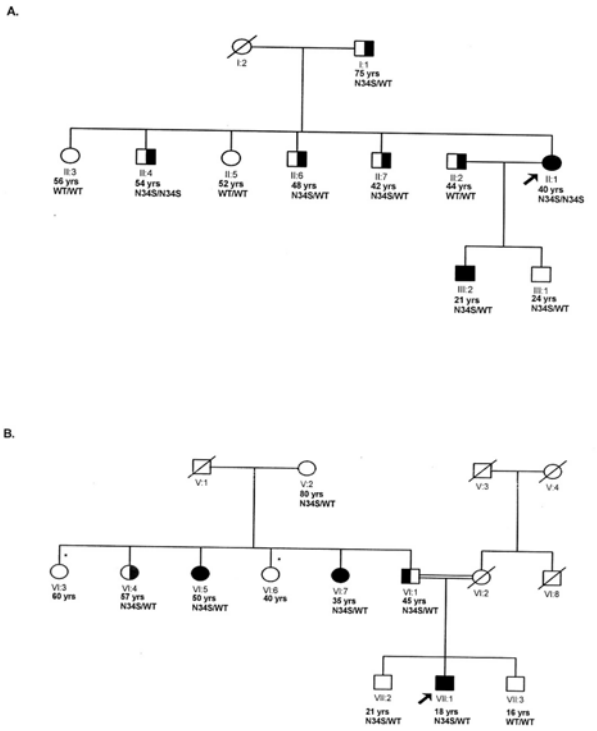
-215 G to



1a. DNA sequencing electropherogram of exon 3 of the human SPINK1 showing A to G transition in a patient with tropical calcific pancreatitis. This mutation leads to an amino acid substitution from Asn to Ser (N34S). Arrowheads indicate the altered nucleotide. **a**. Homozygous state; **b**. Heterozygous state.

1b. DNA sequencing electropherogram of the promoter region of the human SPINK1 showing heterozygous G to T change at nt 215 upstream from translation initiation site (-215G>T) in a patient with tropical calcific pancreatitis. The mutation was absent in 580 alleles from normal individuals. Arrowhead indicates the altered nucleotide.

Figure 2



N34S/N34S, homozygotes; N34S/WT, heterozygotes; WT/WT, wild-type

Chronic pancreatitis

Diabetes mellitus

Both chronic pancreatitis and diabetes mellitus

Proband

* DNA samples not available

Table 1 Characteristics of the study population

	HP	ICP	ACP	TCP	Total
n	37	120	41	106	304
Sex (M/F)	28M/9F	87M/33F	41M/0F	76M/30F	232M/72F
Age of presentation (yrs)	39.5 (31.4-46.6)	27.5 (26.7-30.9)	40.0 (37.1-41.9)	32.0 (30.0-34.8)	31.0 (30.8-33.7)
Age of onset (yrs)	24.5 (18.1-34.5)	23.5 (22.8-27.3)	36.0 (32.9-37.9)	25.0 (25-29.8)	26.0 (26.3-29.3)
Duration of symptoms (yrs)	9.5 (6.7-15.9)	4.7 (3.9-5.4)	4.0 (3.7-5.7)	4.5 (4.2-6.6)	4.2 (4.0-5.3)

Values are median (range 95% confidence interval)

n, number of patients; HP, hereditary pancreatitis; ICP, idiopathic chronic pancreatitis; ACP, alcohol related pancreatitis; TCP, tropical calcific pancreatitis

Table 2 Distribution and status of the PRSS1 and SPINK1 mutations in chronic pancreatitis patients

	HP	ICP	ACP	TCP	Total
n	37	120	41	106	304
PRSS1 mutation*	-	-	-	-	-
SPINK1 mutation	27 (73%)	39 (32.5%)	11 (26%)	45 (42.5%)	122 (40.1%)
N34S	27	38	10	43	118
Homozygote	20	7	1	10	38
Heterozygote	7	31	9	33	80
P55S	-	1	1 (2.4%)	2 (1.9%)	4 (1.3%)
Homozygote	-	-	-	-	-
Heterozygote	-	1	1	2	4

n, number of patients; HP, hereditary pancreatitis; ICP, idiopathic chronic pancreatitis; ACP, alcohol related pancreatitis; TCP, tropical calcific pancreatitis

* Neither the common nor any novel mutation were detected in the PRSS1 gene;

Figures in parentheses indicate percentage

Table 3 Distribution of various clinical parameters among patients with different types of chronic pancreatitis based on N34S SPINK1 mutation status

	HP (n=37)		ICP (n=120)		ACP (n=41)		TCP (n=106)	
	Mutated SPINK1	Mutation Negative	Mutated SPINK1	Mutation Negative	Mutated SPINK1	Mutation Negative	Mutated SPINK1	Mutation Negative
n	27	10	38	82	10	31	44	62
Age at presentation (yrs) (median, range 95% CI)	35.0 (31.5-36.1)	39.5 (36.5-44.3)	24.0 (22.2-28.8)	28.5 (27.8-32.9)	31.0 (28.8-38.2)	41.0 (38.3-43.3)	30.5 (27.9-36)	32 (30.2-36.2)
Age at onset (yrs)* (median, range 95% CI)	23.5 (21.2-29.2)	24.5 (23.3-31.8)	19.5 (17.8-24.2)	25.0 (24.6-29.7)	28.0 (24.2-34.5)	38.0 (34.8-40.0)	25 (22.5-30.4)	25 (24.8-30.7)
Clinical parameters								
Nature of Pain								
Intermittent	18 (74.1%)	3 (30%)	18 (47.4%)	19 (23.3%)	4 (40%)	5 (16.1%)	18 (41%)	23 (37%)
Constant	6 (22.2%)	6 (60%)	14 (36.8%)	54 (65.8%)	4 (40%)	24 (77.4%)	20 (45%)	31 (50%)
Diabetes mellitus#	11 (40.7%)	4 (40%)	4 (10.5%)	15 (18.3%)	3 (30%)	5 (16.1%)	13 (29.5%)	17 (27.4%)
Smoking	4 (14.8%)	3 (30%)	6 (15.8%)	22 (26.8%)	2 (20%)	8 (25.8%)	18 (41%)	12 (19%)
Pseudocyst	4 (14.8%)	2 (20%)	6 (15.8%)	20 (24.4%)	2 (20%)	8 (25.8%)	-	3 (5%)

n, number of patients; HP, hereditary pancreatitis; ICP, idiopathic chronic pancreatitis; ACP, alcohol related pancreatitis; TCP, tropical calcific pancreatitis

* p=0.045 for HP; p=0.177 for ICP; p=0.091 for ACP; p=0.410 for TCP

p = 0.978 for HP; p=0.505 for ICP; p=0.741 for ACP; p=0.858 for TCP

Percentages refer to the proportion of patients within each group

Table 4 Distribution of the N34S SPINK1 mutation in patients with chronic pancreatitis with respect to diabetes mellitus

	HP (n=37)		ICP (n=120)				ACP (n=41)		TCP (n=106)	
	with DM	Without DM	with DM	Without DM	with DM	Without DM	with DM	Without DM	with DM	Without DM
n	15	22	19	101	8	33	30	76	72	232
N34S SPINK1 mutation	11 (73.3%)	16 (72.7%)	4 (21%)	34 (33.7%)	3 (21.2%)	7 (21.2%)	13 (43.3%)	31 (40.8%)	31(43.0%)	88 (37.9%)
Homozygote	7	0	1	6	1	0	3	7	12	13
Heterozygote	4	16	3	28	7	7	10	24	24	75

n, number of patients; HP, hereditary pancreatitis; ICP, idiopathic chronic pancreatitis; ACP, alcohol related pancreatitis; TCP, tropical calcific pancreatitis

Figures in parentheses indicate percentage

Chapter 20

The pathology of fibrocalculous pancreatopathy (CCP)

Balaraman Nair M

Summary

In this chapter, the pathology of fibrocalculous pancreatopathy is covered in detail. In addition, the origin and pathological features of chronic calculous pancreatopathy (CCP), a term with multiple connotations, are also discussed. Extensive study of cases of CCP, several biopsy and a few autopsy specimens show that CCP is not likely to represent the chronic stage of acute pancreatitis. It does not appear that CCP is primarily an inflammatory disease of the pancreas. The exact etiology and etiopathogenesis still elude clinicians, pathologists and research workers. The early stages and further development of the lesions are interesting to study, as the disease does not affect the whole pancreas uniformly. Abdominal pain, calculus, and diabetes mellitus are all events that occur at some stage of the disease. The pathological changes noted, including neural, vascular and interstitial alterations, are all described in detail and their implications are discussed.

Introduction: CCP and the exocrine pancreas

It is not possible clinically to recognize early cases of CCP. But early pathological changes are made out in biopsy specimens and in autopsied cases. The changes in the pancreas are not uniform. Early changes are seen along with late and fibrotic stages and transition can be made out in a satisfactory biopsy specimen.

Grossly pancreas may be normal, enlarged or, atrophic and fingerlike. It may be nodular and felt as a 'bag of stones'. The normally sized pancreas has normal as well as atrophied parenchyma. Abnormally enlarged pancreas is seen in 'lipomatous atrophy', when the entire pancreas is replaced by fat. Some radiologists are able to diagnose this condition in CT and MRI images. Only ducts and islets can be made out, to recognize the organ as pancreas. Staining the entire pancreas with fat-stains can highlight the change.

The changes in the pancreas in CCP are never uniform. The transition from normal to diseased may be abrupt and side-by-side with atrophic and fibrotic stages. The most striking and consistent early change is, disruption of normal architecture. The pancreas presents an 'exploded

appearance' of the parenchyma. There is an exaggerated lobular appearance presenting a 'geographical pattern'.

The disruption results in isolation of groups of acini, single acinus and even single cells, some of them still retaining the bipolar staining. Individual cells are shrunken; some of them have scanty cytoplasm and appear as almost naked nuclei. There are wide gaps separating lobules, acini and individual cells, due to atrophy and disappearance of parenchymal cells. In advanced cases entire lobules may just disappear (lobular, acinar and cellular obsolescence'), leaving only the ducts, areolar tissue, blood vessels, nerves and islets, which help in identifying the organ as pancreas. Lobules may be replaced by duct like structures- 'ductalisation of acini'. Lipomatous atrophy of the pancreas presents a striking appearance. The surviving or hypertrophic islets are seen in a mass of fat and are the only evidence for identyfying the tissue as pancreas. In the final stages of the disease the organ shows fibrous tissue, fat and several normal, atrophic or hypertrophic (regenerated) islets.

Ductal changes

While the acini undergo regressive and atrophic changes, the ducts show atavistic tendency and try to regenerate and replace the lost pancreatic tissue, but stops with regeneration of the islets; very rarely the acini.

The duct of Wirsung and the draining secondary and tertiary ducts show proliferative and metaplastic changes. The duct of Wirsung shows often mucinous and sometimes squamous metaplasia. Mucinous metaplasia is the commonest change noted. Squamous metaplasia is often associated with calculi. When calculi are present there is often periductal lymphocytic infiltration. The secondary and tertiary ducts often show only mucinous metaplasia. Sometimes goblet cells dominate the lining. The ducts are often dilated and plugged with inspissated mucus – 'the mucus plug'. The inspissated mucus plugs in the ducts, form the nidus for formation of calculi. The epithelium of the major ducts may be ulcerated due to the presence of rough and thorny calculi. The epithelium is often torn off during surgery when the incarcerated stone is removed. Persistence of calculi may result in proliferative activity of the ductal epithelium, squamous metaplasia and dysplastic changes.

The proliferative changes used to stop with metaplasia and dysplasia, when death used to occur early in younger patients, due to complications of diabetes mellitus. Since patients of CCP, treated with insulin, now live longer, some of them develop adenocarcinoma of pancreatic ducts. CCP has been identified as one of the causes of adenocarcinoma of pancreatic ducts.

Calculi

Only intraductal calculi have been found, but parenchymal calcification never. There is erroneous usage of the term 'calcification' for calculi. In the early stages of formation of the calculi, by impregnation of calcium carbonate and other materials in the mucus plug, the calculi are soft, friable and are radiolucent. Therefore early calculi are missed by radiological examination and the diagnosis of CCP may be missed. At this stage, along with mucus, the calculus shows presence of desquamated epithelium of the ducts and organic materials, including fibrin. Even some of the hard calculi on decalcification show presence of organic materials, in addition to mucus. The hard and well-formed calculi vary in size and shape. They may be like gravel, round, oval, coralloid, elongated and staghorn-like or in the shape of the ductal lumen in which they are formed. Some of them are as big as the dilated duct of Wirsung. They are arranged as beads along the length of the main duct, with dilatation of the intervening portions, very explicitly demonstrated by ERCP. Intermittent calculous obstruction causes 'lake-like' dilatation of the duct of Wirsung, demonstrated by contrast radiography. The hard calculi contain not only calcium carbonate but also traces of several other materials and show a very striking appearance by X-Ray diffraction study. Traces of substances like iron, magnesium and selenium have been demonstrated. This suggests that the formation of calculi in CCP is not by a simple process of dystrophic calcification of the mucus plug. It is also important to note that in acute and chronic pancreatitis as well as in other pancreatic diseases, including alcoholic pancreatitis, formation of calculi is not so common. Parenchymal calcification occurs in cases of acute pancreatitis following fat necrosis, but never in CCP. In the early stages of formation of the calculus (soft calculus) they cannot be demonstrated by x-ray examination and patients seldom complain of pain. The pain is often due to incarceration of the

ducts with calculi, causing ductitis. Hence the early stage of the disease is missed clinically, when pain and radiologically demonstrable calculi are absent. At the same time the disease, especially destruction of exocrine pancreas may be advanced.

Insular changes (Nesidioblastosis)

The changes in the islets are most remarkable and a consistent finding in all cases of CCP. It is even an indicator that one is dealing with a case of CCP, in the absence of any other pancreatic disease. The insular changes are mostly seen in areas where there is advanced acinar atrophy. There are small atrophic islets, normal islets and markedly hypertrophic islets. Some of the islets are very large and vary in shape. The total atrophy of the exocrine pancreas and the remarkable preservation of the islets present a 'bunch of grape appearance` of the islets.

There is extensive nesidioblastosis. This is an attempt on the part of the pancreas to regenerate. The process starts at the intercalated ducts. Most of the regenerated islets show their origin from the ducts, which are seen at the periphery of the newly formed islets.

The regenerated islets and even the atrophic ones are rich in B-cells and produce insulin. In fact the regenerated islets contain more B-cells and are loaded with insulin. Even the atrophic islets and sometimes the intercalated ducts from which the islets regenerate, contain insulin.

Inflammatory cells

Inflammatory cells are not invariably found in all stages of the disease. They are often seen when calculi appear in the ducts and are seen mainly periductally. Diffuse inflammatory changes are seen in some cases. This is an inconsistent finding. The predominant cells are lymphocytes. Occasionally plasma cells and eosinophil cells are seen, but neutrophilic leucocytes and macrophages or granulomas are never found. In several cases inflammatory cells are barely found at the site of the early lesion. The presence of inflammatory cells in CCP is so inconsistent that the role of inflammation in the etiopathogenesis of the disease is not confirmed and is unlikely.

Neural changes

Neural changes are consistent and are very striking in advanced cases. In normal pancreas nerves are seldom seen in the parenchyma. In all cases of CCP prominent nerves are seen, often associated with ganglion cells. This neuroendocrine relation is relevant in the regenerative process of islets. A very close association is seen between these prominent nerves, ganglia and regenerating islets. .

Vascular changes

Pancreatic arteries often show thick walls and minimal narrowing of the lumen. Sclerosed arteries are seen in advanced CCP. The exact significance of these changes is not known.

Changes in the interstitium

The changes in the interstitium are not consistent. Though the disease is often called fibrocalculous pancreatopathy, fibrosis is not consistent. In the early stages, fibrosis is seen mostly periductally or none at all. Early fibrosis is often non-collagenous and consists of loose fibrous tissue. Later on the fibrosis may be so advanced as to produce 'cirrhosis' of the pancreas. The fibrosis may be so severe that along with the parenchymal atrophy, the organ is almost a thick cord-like structure, filled with stones. Focal deposition of fat in areas of parenchymal atrophy is not rare in CCP. In total parenchymal atrophy the entire organ may be replaced with fat, sparing the ducts and a few regenerated islets. Even in extensive fibrosis, a few surviving islets may be found.

The pathological changes in CCP are not consistent. They depend on the stage of the disease and the site from where the biopsy is taken. All stages of the disease may be seen in the same pancreas.

Discussion: Chronic calculus pancreatopathy: various connotations

The term Chronic Calcific Pancreatitis is a misnomer. There is no parenchymal calcification in any of the cases studied and there is

histological evidence that inflammation is not a constant finding in all cases. Ever since its first description by Zuidema from Indonesia in 1959, there have been several reports of the disease under different names. The first report of CCP along with other cases of chronic pancreatitis was in 1946 by Comfort, Gambill and Baggenstos, again in 1948 by Gambill, Comfort and Baggenstoss. There is also a report in 1948 by Janowitz and Dreiling. In 1960, Gambill, Baggenstoss and Priestly reported 27 cases, which they had studied from 1939 to 1943. Kini reported the first case in India from Bombay (now Mumbai). There is a report by Fitzgerald et al of 53 cases studied from 1952 to 1960. The first case from Kerala was presented by Kesavan Nair, a reputed Surgeon and Professor of Surgery at a conference in Agra in 1937. There is obviously a mix up of all cases of chronic pancreatitis and other pancreatic diseases, in the cases reported earlier.

The largest number of cases have been reported from Kerala, a small state in the southern most part of India. Geevarghese had studied and reported more than 1000 cases from Kerala alone and is rightfully credited with the wide recognition of the disease CCP, in India. He has vividly described the clinical symptoms and some of the concepts of aetiopathogenesis and pathology of the disease. This was at a time, when surgeons in India did not confidently operate on pancreas. Biopsies were rare.

The disease has been reported under the following names: chronic calcific pancreatitis (CCP), fibrocalcific pancreatitis (FCP), chronic calcified pancreatitis,chronic relapsing pancreatitis, chronic progressive pancreatitis ,fibrocalculus pancreatitis, tropical pancreatitis. (TP), nonalcoholic pancreatitis, hereditary pancreatitis, Afro-Asian pancreatitis, idiopathic pancreatitis, chronic calculus pancreatopathy and fibrocalculous pancreatopathy.

The only factor common to all these terms is ‘chronic’ and is the only factor true to this disease. All these terminologies for CCP, came from the imperfect knowledge of the etiopathogenesis of the disease. There are several cases without any evidence of inflammation, fibrosis and invariably there is no calcification.

At the International Workshop on 'Types of diabetes peculiar to tropics' in the year 1995 at Cuttack, it was resolved to accept the terminology of 'Chronic Calculus Pancreatopathy' (CCP).

CCP is a non-inflammatory disease of the pancreas, of poorly understood aetiology, with malnutrition at some stage of life contributing, affecting young adults, clinically characterized by recurrent abdominal pain, brittle or resistant diabetes mellitus, rarity of ketosis and pathologically characterized by smoldering, focal, lobular or segmental atrophy of exocrine pancreas. These are followed by other lesions like nesidioblastosis, mucus plugs and calculi in the ducts. The Marseille symposium defined CCP as 'chronic pancreatitis characterized by lasting damage, whether or not the cause of the disease is removed, sclerosis with destruction and focal, segmental or diffuse disappearance of the exocrine pancreas and sometimes overlaid with acute ones'. If the 'acute ones' suggest acute pancreatitis, these do not conform to classic cases of CCP. If this 'acute ones' suggest clinical onset of abdominal pain or other symptoms, it is acceptable. The early stage of the disease has not been recognized clinically. Four criteria have been defined (Mohan et al) for clinical recognition of the disease:

1. Patient of tropical origin
2. Diabetes (WHO criteria)
3. Evidence of pancreatitis as shown by calculi(by imageology), abdominal pain, steatorrhoea, abnormal pancreatic function tests and
4. Absence of other causes of pancreatitis

Often all these criteria may be absent. Diabetes or detection of calculi on routine screening may be the first clinical evidence of the disease. Diabetes may be an early presenting symptom. Bank has reported the follow up of 35 patients who showed no calculi at the time of presentation, but developed them later on. The occurrence of decreased glucose tolerance in this group increased from 70% to 91% after the appearance of calculi, indicating further destruction of the endocrine tissue.

The etiology of the disease has eluded Clinicians, Pathologists and Research workers alike. The pancreatic structure and function are influenced by a number of nutritional factors- proteins, carbohydrates,

fat, trace-elements and micronutrients. The pancreas has a higher turnover of proteins compared with other organs. It is only natural that pancreatic injury occurs in qualitative or quantitative protein deficiency, as in Kwashiorkor. The pancreas in Kwashiorkor is small, shrunken and fibrosed.

Epidemiological studies and experimental work on bonnet monkeys (Macaca radiata) have suggested that malnutrition (not undernutrition), especially protein malnutrition, can play a role or at least can be a major contributory factor. Bonnet monkeys were fed on an isocaloric low protein, normal carbohydrate diet. Another group was fed on low protein and high carbohydrate diet, containing tapioca-starch and cornstarch as carbohydrates. These animals showed pancreatic changes identical to CCP. The pancreas showed no inflammatory changes. This experiment is the first monkey model for production of pancreatic disease.

The toxic effect of tapioca in the diet has been postulated as a cause of the disease. Cassava (Tapioca, manihot) is eaten in large quantities in Kerala, Uganda, Nigeria, Indonesia, Malawi and Thailand, where CCP is prevalent. Cassava contains cynogenic glycosides, linamerin and lotaustralin. Of these, linamerine was suspected to be the causative factor. Cyanogens impair the function of enzymes like superoxide dismutase, which scavenge and prevent cell injury by free radicals. Chronic cassava ingestion in rats up to one year did not produce CCP. The epidemiological and experimental findings are not in favour of cassava ingestion as a cause of CCP. More over the disease has been found in populations not consuming tapioca. The McMillan and Geevarghese hypothesis has not been substantiated.

The role of trace-elements has been recognized. Methonine, zinc, selenium and copper are deficient in malnutrition. The deficiencies of these are not clinically obvious unless studied objectively. Feeding rats on zinc deficient diet has produced changes in pancreas. A copper deficient diet has produced selective acinar injury, sparing islets and ducts. Similarly deficiency of selenium and magnesium in the diet has been shown to produce pancreatic acinar injury. Cerium has been postulated to produce endomyocardial fibrosis in experimental animals. Tapioca contains Cerium.

Ductal obstruction has been suggested as the etiology. Obstruction due to stasis produced by infections and inflammation caused by bacteria, viruses or parasites, has been postulated as cause of CCP True that many of the pathological changes noted are similar to the ductal obstruction produced experimentally but it is not proved to be the aetiological factor. The changes in the fully evolved and clinically recognisable disease are due to ductal obstruction produced by the calculi in the duct of Wirsung. The theory, that anomalies of the sphinctor of Oddi, spasm or oddities cause CCP, has not been substantiated surgically or by imageology.

Hyperparathyroidism as a cause is common in acute pancreatitis and parenchymal calcification.

An autoimmune process has been suggested but without any proof.

As early as 2001, the role of genetics in the causation of CCP, has been studied. There are more than 300 indexed reports on this topic. Recently there has been a re-emergence of this hypothesis. Available evidence shows that only about 23%- 25% of CCP cases have an abnormal mutation of the SPINK I gene. David C. Whitcomb and co-workers at the University of Pittsburgh, have studied the mutation of the SPINK I gene, in the 'family x'. 'Family-X' is the largest pancreatic cancer family ever studied. Out of 20 family members 9 died of pancreatic cancer, including 5 out of 6 brothers. Every member of the 'family x' with pancreatic carcinoma or its precursor, harbored a specific genetic marker on the long arm of chromosome 4, where the single gene mutation resulting in pancreatic carcinoma is believed to exist.

There are two common and more than six uncommon cationic trypsinogen gene mutations associated with carcinoma of pancreas. The two major mutations are cationic trypsinogen 'R122H' and 'N291".

The SPINK I gene initiates the production of a specific protein- 'the pancreatic trypsinogen inhibitor', which prevents activation of trypsinogen to trypsin. When SPINK I gene mutation occurs, trypsinogen gets activated to trypsin which acts on pancreas, causing recurrent acute pancreatitis. Mutations of SPINK I gene is considered as the most significant genetic risk factor.

In 2003 the Asian Institute of Gastroenterology and the Center for Cellular and Molecular Biology (CCMB) in Hyderabad, reported the occurrence of SPINK I gene mutation in Indian patients of CCP. In their study of 120 patients, this gene mutation was noticed in 45 % of cases. This high incidence is possibly due to the small group of patients in their study.

Gene mutation causing pancreatic disease similar to cystic fibrosis, has been identified. This Cystic Fibrosis Transmembrane Conductance Regulator Gene (CFTCR) mutation produces lesions in pancreas similar to cystic fibrosis. This gene mutation affects hydration of the secretions of pancreas and other organs like the lung. Mutation causes prevention of thinning of the secretion, leading to inspissation and formation of the tenacious mucus plug.

Currently work has been going on, in different centers in India, to find out the involvement of the SPINK I gene mutation, in the aetiopathogenesis of CCP in our population. It is doubtful whether this gene mutation plays a role in the genesis of CCP. According to this hypothesis CCP is then, the chronic stage of acute pancreatitis. There is no clinical or pathological evidence to show that CCP is the chronic state of acute pancreatitis. Therefore the SPINK I gene mutation theory is not tenable.

Comparing the role of the two genes, it is more possible that the CFTCR gene has a role in the genesis of CCP and not the SPINK gene.

Alcoholism has never been proved to be the cause, in this studied series. There are several reports of alcoholic pancreatitis being included in CCP. Sarles in his earlier reports has considered alcoholic pancreatitis also as CCP. He has mentioned that 'CCP is frequently of alcoholic origin'. The pathogenesis of alcoholic pancreatitis 'remains elusive'. The postulated mechanisms are 1. lack of 'stone protein' and 2. primary acinar injury. Autopsy study of the affected pancreas supports the latter hypothesis. But the changes in alcoholic pancreatitis are diffuse and affect nearly the entire pancreas and not piece meal as in CCP. There is age and sex difference. Nesidioblastosis and calculi are not as frequent.

Current concept is that CCP is a multifactorial disease

Clinically, it is almost impossible to detect early cases, since patients present with abdominal pain or diabetes mellitus or calculi, often in an advanced stage.

Pathologically it is possible to detect early stages, since in many cases the progression of the disease is not uniform and early pathological lesions can be made out along with the most advanced lesions. Every part of the pancreas is involved in advanced cases. The pathology described, is the result of study of several biopsies and a few autopsies.

Gross changes

Gross features of the pancreas in CCP; have been made out by imageology, during surgical intervention and from a few autopsy cases. The size of the pancreas may be normal, increased or decreased. In early cases there is no alteration in the size of the pancreas since there is little parenchymal loss. Increase in size is usually seen in 'lipomatous atrophy' of the pancreas. Radiologists are able to recognise this lesion due to the alteration of the density of the image and the presence of the calculi. The pancreas is enlarged, soft and yellow and may look like a mass of fat. Only microscopic examination will reveal the mass as pancreas by the presence of scanty exocrine glands, plenty of islets and calculi. In most of the cases the pancreas is shrunken and firm. There were cases where the pancreas was finger-like and hard due to fibrosis and the presence of calculi in the ducts. The ductal dilatation may be so severe that they form cystic spaces filled with stones. Section of the normal sized pancreas shows hard areas and presence of calculi. Many of the ducts may show mucus plugs. In advanced cases the most striking feature is the presence of multiple calculi of varying sizes, shapes and consistency. There may be nodular appearance and feel, which surgeons per-operatively, may mistake for carcinoma.

Microscopic appearance

Acinar changes: The early stage of the disease has not been recognized

clinically and so not biopsied. But changes from normal to early disease and to severe stages can be recognized in biopsies and autopsies. The exocrine reserve of the pancreas is found up to the very late stage of the disease. This accounts for the presence of exocrine function in majority of cases studied.

The earliest changes are noticed in the acini. There is a lobular distribution of the lesions. In early cases, the affected acini or lobules are seen side by side with histologically normal acini and lobules. The patchy distribution of the lesions is a constant characteristic of CCP. The histological characteristics of all cases of CCP are identical, varying only in severity. It has been reported that in cases where there is no radiological evidence of calculi, biopsy showed identical pathological changes, and when these cases were followed they showed radiological evidence of calculi.

Normal acini and lobules persist for a long time along with obsolescence of several lobules. The disappearance of large masses of acini without evidence of necrosis could be due to accelerated apoptosis, followed by phagocytic removal. The apoptotic removal of acini and ductal proliferation has been demonstrated in experimental animals. But few apoptotic cells and practically no phagocytes have been observed in CCP. There was no necrosis of the parenchyma or fat necrosis, as occurs in acute pancreatitis. All other changes are seen later, after acinar changes occur. Disruptions of the acini are noticed early and are very similar to those seen in ductal obstruction.

The youngest case that has come to the study, is a newborn child admitted with severe hypoglycemia for which total pancreatectomy was done. Study of the pancreas showed early acinar changes in the pancreas identical to the early changes seen in CCP. There were lobular lesions where acini had atrophied or disappeared and ducts persisted. No calculi were seen. There was extensive nesidioblastosis resulting in near fatal hypoglycemia. Liver biopsy was done later and showed changes similar to biliary cirrhosis, suggesting the possibility of neonatal odditis or ductal obstruction. Unfortunately the pancreas was not available for detailed study. (Kind permission and personal communication from Dr. Chandrika, AIMS, Cochin). The lobules, groups of acini, single acinus and single

cells are seen isolated. But often there is no fibrosis. Several lobules, groups of acini, individual acinus and even single cells just disappear, as seen in 'glomerular obsolescence' in renal diseases. The bipolar staining is maintained till ultimate cell death. Electron microscopic studies by Sarles et al of the histologically normal areas of pancreas in established cases of CCP, showed decrease in zymogen granules with concomitant increase in the number of prozymogen granules, indicating dysfunction at molecular level. The mitochondriae were normal, but the rough endoplasmic reticulum and the golgi bodies were dilated. The surface area of the cells, nucleus and nucleolus, is augmented indicating hyperfunction with regard to enzyme secretion. The later changes are possibly due to cell exhaustion, resulting in atrophic changes and apoptosis. This also accounts for the inconsistent enzyme changes seen in CCP.

'Ductalisation' of the pancreas has been observed in several cases. At this stage of the disease, there is no evidence of any inflammation or fibrosis. The atrophic lobules, acini, and cells are separated by large spaces indicating atrophy. The lack of evidence of inflammation should draw attention to other pathological processes, possibly metabolic disturbances like malnutrition, rather than under nutrition. The lack of under nutrition has led many to suggest that nutrition has no role in the genesis of CCP. There are two factors in favor of malnutrition. First, the changes in the pancreas are similar to those seen in Kwashiorkor. Secondly, malnutrition or metabolic changes occurring at any stage of life, particularly during childhood, may have permanent adverse effects on metabolism. It is likely that CCP may be a form of malnutrition, though there may be no evidence of it, at the time of presentation. This may be in the form of protein malnutrition, deficiency of any of the amino acids or trace elements.

There are large areas where the acini may disappear and in long standing cases, the pancreas may be converted to an atrophic finger-like structure with many calculi, forming a 'bag of stones'.

In some cases the atrophic pancreas may be replaced by fat. The pancreas is bigger than normal due to the enormous deposition of fat (lipomatous atrophy of pancreas). Lipomatous atrophy of the pancreas in CCP has been reported as early as 1970. Radiologists are able to diagnose this

fatty change in CT and MRI scans. The changes that lead to lipomatous atrophy of the pancreas is not known, though fat deposition has been found in some cases of CCP. Only the surviving islets help to identify the organ as pancreas.

The extent of fibrosis varies. It may be totally absent, or the fibrosis may be so severe as to create a 'cirrhotic pancreas'. No case has shown features of acute pancreatitis or pancreatic necrosis. It is an error to consider CCP as a chronic stage of acute pancreatitis.

Ductal changes

In available autopsy cases there have been no evidence of odditis. Experimental partial obstruction of the duct of Wirsung produces changes identical to advanced stage of CCP.

The ductal cells play an important role in the secretion of fluids, electrolytes and mucin. In experimental animals, labeling with tritiated thymidine has shown that the proliferative activity of ductal cells is the same as that of acini and islets. Of all the components of the pancreatic tissue, the ducts preserve their capacity to regenerate and proliferate, especially the intralobular ducts. They proliferate more profusely under several pathological stimuli. During the neonatal period the ducts proliferate and produce islets. In some pancreatic diseases like CCP, the ducts may give rise to new islets and also cause the acini to form duct-like structures. ('Ductalisation' of the acini)

In CCP the most striking changes are seen in the ducts. In well-established cases, the ducts show constrictions and 'lake-like' dilatations. This change is due partly to atrophy of the parenchyma and partly to the focal ductal obstruction by calculi.

The duct of Wirsung shows metaplastic changes. The commonest changes are mucinous. Squamous metaplasia is infrequent. Desquamation of the epithelium is often seen in the presence of calculi. The first change, that takes place, is mucinous metaplasia, a change that may extend to the secondary and tertiary ducts. This change may be seen in ageing pancreas and in induced partial obstruction to the

main duct, in experimental animals. This initiates altered secretion and the formation of 'mucus plugs' ('chronic catarrh'). Sarles has suggested that the 'specific pathogenic mechanism in CCP is the precipitation of secretory proteins in the ducts', but failed to recognize that the abnormal protein secretion follows acinar changes. His hypothesis is that CCP is an inflammatory disease. As the secretion of mucus becomes thick and inspissated, the ducts get obstructed and this leads to further changes in the exocrine pancreas. It is not definite whether the mucinous metaplasia of the ducts is a sequelae of acinar changes or this occurs concurrently due to the same initiating factors. The obstruction to the flow of pancreatic juice has been attributed to the metaplasia. But the extent of metaplasia and even the papillary formations produced have never been noted to be the cause of obstruction to the flow of pancreatic juice.

Squamous metaplasia is not as common as mucinous metaplasia. Squamous changes are seen in the ducts lodging the calculi and are due to the irritation caused by them. These changes are seen in the duct of Wirsung lodging large calculi.

Ductalisation of acini occurs in some cases. The exact mechanism is disputed. It was postulated that the acini undergo necrosis and are replaced by ducts, but there is no necrosis in CCP. Others have suggested that the acinar cells atrophy and assume shape of ducts. Apoptosis of acinar cells has also been suggested as the mechanism for their replacement by ductal cells.

Dysplastic changes are seen in long standing cases, ultimately leading to adenocarcinoma of pancreatic ducts. Mitoses are often seen in the ductal epithelium. Opitz first reported the association of pancreatic lithiasis and carcinima in 1901. Dysplastic and neoplastic changes are seen only in long standing cases who survive due to insulin administration. There is definite clinical evidence that CCP is one of the causes of ductal adenocarcinoma of the pancreas. Rajan has reported his experience with surgical intervention in cases of CCP, in 64 cases done mainly to alleviate pain. He found 9 cases had adenocarcinoma on biopsy examination. Philip Augustine and Ramesh have reported 22 cases of adenocarcinoma of pancreas among 225 cases of CCP. This was rare in the earlier cases reported, since death due to complications

of uncontrolled diabetes occurred early. Carcinoma associated with lithiasis is distinct, in that these cases occurred at younger age (average 40 years) and pancreatic calculi are always present along with diabetes. The chronic irritation produced by calculi, causes dysplasia of the ductal epithelium ending in adenocarcinoma in surviving patients.

Mucus plugs

It is possible that the 'mucus plugs' contain substances other than mucus, especially trace elements, as shown by stone analysis. The mucus plugs are mainly formed in the duct of Wirsung. They are also seen to occur in the major branches. They contain a lot of proteins, mainly glycoproteins, containing phosphorylated residues, an undetermined carbohydrate moiety ('Stone protein' – Sarles), a few cells and sometimes fibrin. These can be demonstrated in some of the decalcified calculi. The composition of all pancreatic calculi are the same.The mechanism of formation of the mucus plug is not certain, but is not due to inspissation of a thin mucus secretion by the metaplastic ductal cells. The initial secretion itself appears to be thick and viscid. It is possible that this altered secretion occurs due to the changes in the acini and mucinous metaplasia of the ductal epithelium.

The calculi

The first description of pancreatic calculi has been by De Graaf in 1667. There were reports of the disease as pancreatic lithiasis by Opitz (1901), De Graaf (1914), Mayo et al (1936) and Comfort et al (1946). The first description of pancreatic calcification and diabetes has been attributed to Cawley in 1788.

CCP has never shown parenchymal calcification. The 'diffuse calcification' reported by Sarles has never been observed in our cases. Small cystic dilatations have been observed but the pseudocysts developing in the pancreas and even outside the pancreas (Sarles) have never been observed. These are possibly cases of pancreatitis or fibrocystic disease of the pancreas and not CCP.

Calcium apatite crystals appear in smaller ducts before calculi appear in

larger ducts, as demonstrated by polarization microscopy. It has been demonstrated that the calcium ions in the pancreatic secretion are in equilibrium with those of diffusible calcium in the serum. Hence any change in the water content or pH of the pancreatic juice can result in precipitation of calcium and formation of 'sand'.

After the initial changes in the exocrine pancreas, the formation of calculi is an important event in the progression of the disease. The presence of the calculi leads to 'obstructive pancreatopathy'. The changes are similar to those produced by ductal ligation in the experiments of Banting and Best – a selective atrophy of the exocrine pancreas, leaving the islets and neurovascular components intact. Decalcification of the soft calculi shows presence of cell debris, fibrin and other proteinaceous substances. Spheres of eosinophilic, amorphous material, similar to the corpora amylacea of prostatic glands, have been reported. The elemental analysis of stone by scanning electron microscopy, 'energy dispersive x-ray fluorescence' (EDXRF) and 'fluorescent spectrography', have shown the presence of iron and several trace elements.

The stone has a central nidus with an outer shell. The nidus shows a network of fibers and no calcium salts. It contains iron, chromium and nickel. Seventeen other trace elements have been detected by EDXRF. The shell is formed of calcite crystals. The iron could be from the lactoferrin of the pancreatic juice. There is periductal inflammation and fibrosis around the ducts containing calculi, possibly due to irritation by the calculi. The calculi induce metaplastic, and dysplastic changes. They vary in size, shape and consistency. The largest reported calculus is 6.1cms long. A Calculus weighing an unbelievable 200gms or more has been reported by Sarles. The shape and size of the calculi depend on the ducts where they are formed. The variation in size, consistency and shape depend on the ductal size, and duration. The early ones are often soft when they are not completely impregnated with calcium carbonate. Their consistency varies from soft to bony hard. They appear smooth, faceted and often coralloid, depending on the pattern of deposition of mineral on the mucus plug. The coral shaped calculi often get incarcerated in the ducts and their removal results in removal of the lining epithelium of the ducts. These are the ones that cause irritation, metaplasia and dysplasia, leading ultimately to carcinoma.

Obstruction caused by calculi leads to further atrophy of the exocrine pancreas. The changes seen in ductal obstruction are similar to those induced experimentally. There is selective atrophy of the acini. All the other components survive till the late stage of the disease. The irritation produced by the calculi also produces periductal inflammation leading to infiltration by lymphocytes occasionally by plasma cells and eosinophil cells. Fibrosis is often seen around the ducts. There are cases in which there is extensive fibrosis, which has given the disease the name 'fibrocalculous pancreatopathy'. But there are several cases in which fibrosis is minimal or entirely absent. It is not possible to suggest why fibrosis is present in some cases and entirely absent in others.

The pain in CCP is due to calculus, similar to renal colic, but less severe and is of dull aching type. There is evidence of neuritis in some, but not in all cases.

Islets of Langerhans

The most striking and constant changes in CCP are seen in the Islets. There are a number of pancreatic diseases, including malignancy, in which regeneration and formation of new islets occur – nesidioblastosis. It was Laidlaw who coined the term and reported in 1938 the occurrence of nesidioblastoma. In CCP there is extensive nesidioblastosis. The newly formed islets contain A-cells and are rich in B-cells. There is a controversy whether B-cells or A-cells predominate.

The study of several cases by IHC for insulin secretion has shown that the B-cells predominate and are seen through out the newly formed islets. Some of the newly formed islets are several times bigger and are of various shapes, compared with normal islets. When there is such striking nesidioblastosis, why the diabetes? The quantum of islets regenerated and the insulin produced are insufficient to replace the islets destroyed. The nesidioblastosis that occurs in pancreatic diseases like malignancy accounts for the hypoglycemia encountered in some of them. Hypoglycemia occurs also in experimental induction of carcinoma pancreas, in partial resection of pancreas and in experimental partial obstruction of pancreatic ducts. The brittle diabetes occurring in some cases of CCP is also due to nesidioblastosis.

The origin of the progenitor cells of the newly formed islets, has been extensively studied. In the Syrian hamster, there are intercalated (intralobular), peri insular and intrainsular ductules. The peri insular and intra insular cells form undifferentiated cells (islet cell precursor cells) and are capable of proliferating and differentiating into B-cells. Exhibition of nitrosoamine for induction of adenocarcinoma of pancreatic ducts, show that these precursor cells are the ones stimulated early and the neoplastic process is associated with nesidioblastosis. The experiments of Yoichi Konishi et al in the production of pancreatic ductal adenocarcinoma, by feeding Syrian hamsters with diethylnitrosamine and other amines, have shown profuse nesidioblastosis. Whether these precursor cells are undifferentiated stem cells of peri insular and intra insular cells or the differentiated ductular cells, has been disputed. Rosenberg et al induced islet cell differentiation and nesidioblastosis in Syrian hamsters by partial ductal obstruction. By use of tritiated thymidine they have shown that the endocrine cell differentiation occurs by migration of cells from ductules, thus reproducing the normal ontogeny of B-cells from the ductular cells. There is ample histological and IHC evidence that in CCP the nesidioblastosis occurs from lining cells of intercalated ductules. Some of the ductal epithelial cells in CCP also show immunoreactivity for insulin.

What is the stimulus for nesidioblastosis? The experiments of Rosenberg and others, on Syrian hamsters have convincingly shown that partial obstruction of duct of Wirsung induces nesidioblastosis. In the Rosenberg procedure, wrapping the pancreatic head loosely by a 2.mm.wide sterile tape produces partial obstruction. This procedure induced nesidioblastosis and hypoglycemia. Partial ductal obstruction has been shown to reverse the diabetes induced by islet destruction by alloxan and the selective destruction of the B-cells by administration of streptozotocin. This proves that partial obstruction is an adequate stimulus for inducing nesidioblastosis. It has been suggested that a substance called 'ilotropin' induces the ductular proliferation. Will Rosenberg procedure be a surgical cure of type II diabetes? Who knows? Sarles has reported a nesidioblastoma in a woman who had partial pancreatectomy earlier. There was periductal fibrosis. Fibrotic changes do induce endocrine cell proliferation in other organs also. In the fibrosed appendix carcinoid tumor develops, and in the lung, neuroendocrine tumors occur in response to fibrotic lesions. The ductal obstruction produced by calculi and fibrotic strictures are responsible for nesidioblastosis in CCP. Endocrine tumourlets

have been described in fibrotic pancreas. The experimental induction of adenocarcinoma and the production of nesidioblastosis in these animals is a process of synchronous. Hyperinsulinemia has been reported secondary to diseases of pancreas. The impetus for this nesidioblastic response is considered to be the destruction to acini. It is possible that the pancreas makes a futile attempt to regenerate and replace the destroyed acini by regeneration, but stops with the differentiation to islets. There are reports that the regenerative process may result in production of acinar cells with zymogen granules. The presence of ductalisation of the pancreas in CCP is thought to be due to regeneration of the ducts. Mitosis has been seen in the ductal and ductular differentiated cells. This observation is against the hypothesis of neogenesis from stem cells.

Hypoglycemia

Spontaneous hypoglycemia has been reported in cases of CCP. Some patients develop insulin resistant hyperglycemia and others a sudden intolerance to massive doses of insulin. The cause of hypoglycemia could be easily explained on the basis of the nesidioblastosis seen in almost all cases of CCP. It has been shown that the newly formed islets are loaded with insulin. Possibly in some cases the amount of insulin released is delayed or prevented from release. In hypoglycemic conditions, the hormone is released in excess.

The hyperglycemia is often due to the massive destruction of the islets and the total mass of islet cells regenerated is inadequate to produce sufficient insulin. Possibly the irregular release of insulin from the nesidioblastic islets is responsible for the brittle diabetes. The massive dose of insulin required by some patients could be due to presence of anti-insulin antibodies, receptor defect on the cell surface or failure of intracellular glucose utilization. It has been observed that during nesidioblastosis there is an excess of B-cell production, as demonstrated by IHC, and deficiency of glucagon due to destruction of the islets. Patients with pancreatic diabetes have normal resting insulin levels, but when challenged with glucose their insulin response was low and delayed, showing low insulin reserve. Similarly glucagon reserve in CCP patients has been found to be low and in some patients severely low.

The transformation of ductal cells to islet cells can be vividly demonstrated in the pancreas of CCP. Apart from the concept of ductular origin of the islets there is a little known neuroendocrine origin. According to this concept, the islet cells are not of endodermal origin from the gut, but from a different category of cells derived from committed neuroendocrine precursor cells (Pearse). According to this hypothesis, the endoderm contains cells, which retain their neuroectodermal status, and are committed to neuroendocrine function. In CCP there is morphological evidence to this association. Almost all cases will show this neuroendocrine association. There is remarkable increase in the number of nerves and ganglia in CCP.

Vasculopathy

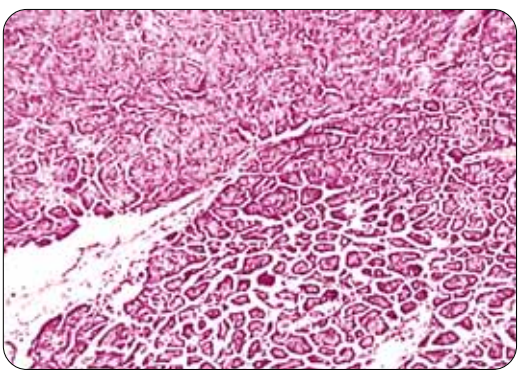
Vasculopathic changes have been noted in the arteries and arterioles of pancreas, but retinopathy, nephropathy and atherosclerosis have not been reported in CCP, possibly due to early death of the patients. Reports show, decreased tendency for organ related vasculopathy except in pancreas. Thickened arteries have been noted by many workers and in my studies. The entire vessel wall is thickened, but there is no arteriosclerosis or atherosclerosis. It is mostly a medial muscular proliferation. The rarity of atherosclerosis could be due to decreased serum lipid levels consequent to the low lipase secretion and reduced absorption of fat.

We know what happens to the pancreas, but not why or how it happens in CCP.

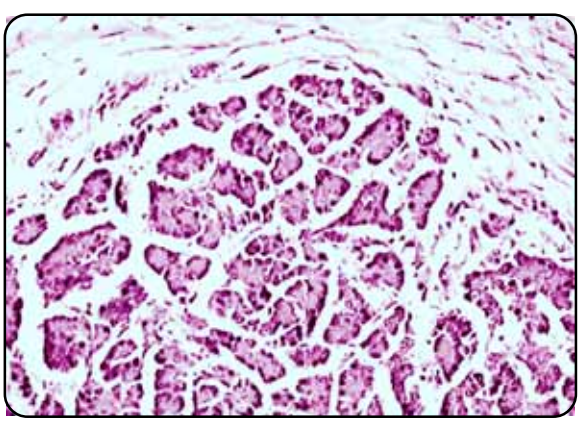
Legends to figures

(All photomicrographs are taken from paraffin sections of 5u thickness, stained with haematoxylin and eosin, except those of IHC for insulin (B cells) and the Energy- dispersive x-ray fluorescence photomicrograph of the calculus).

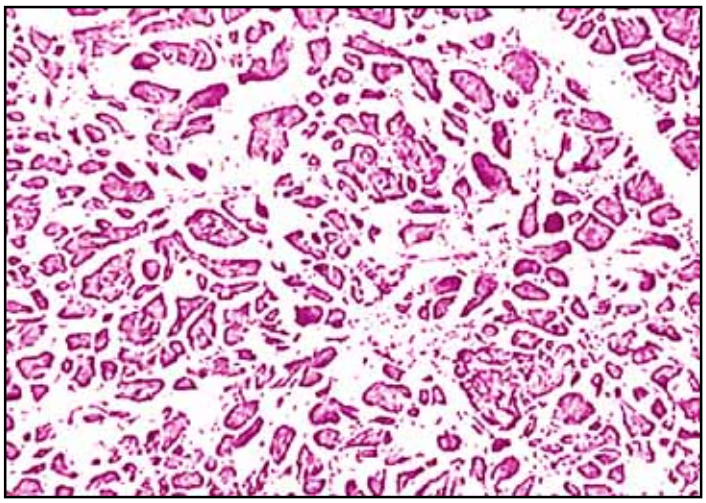
1. Early stage of CCP. Normal pancreas is seen at the top and the disrupted lobule below. Groups and individual acini are separated by empty spaces due to acinar atrophy. There is no inflammation or fibrosis at this stage. These are similar to the changes seen in Kwashiorkor and in partial ductal obstruction in disease and in experimental animals.



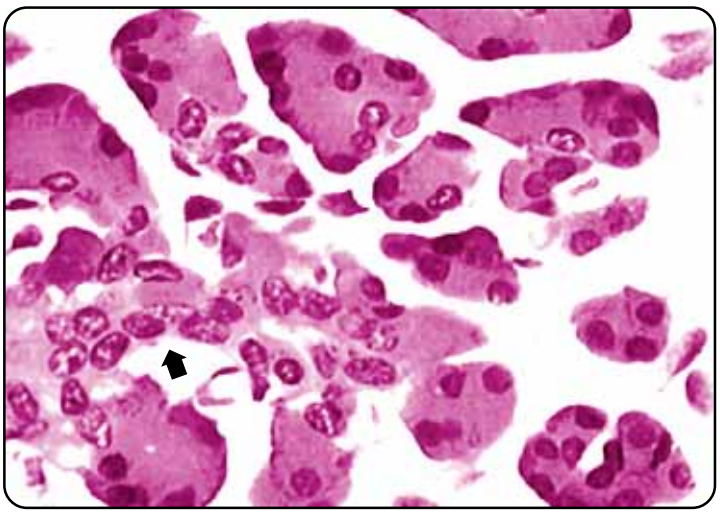
2. An atrophic lobule with disruption of the architecture and early fibrosis. The lobular outline is maintained by fibrous bands at the periphery.



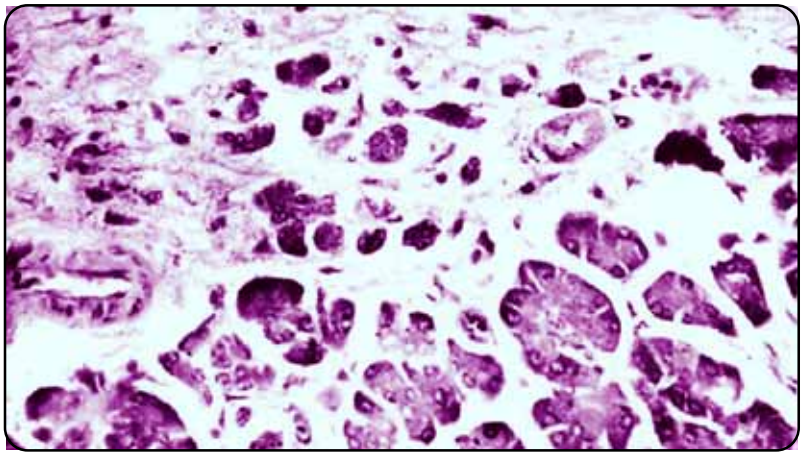
3. 'Exploded' appearance of the pancreas in CCP. Lobules, individual acini and cells are separated by empty spaces. There is little inflammation or fibrosis.



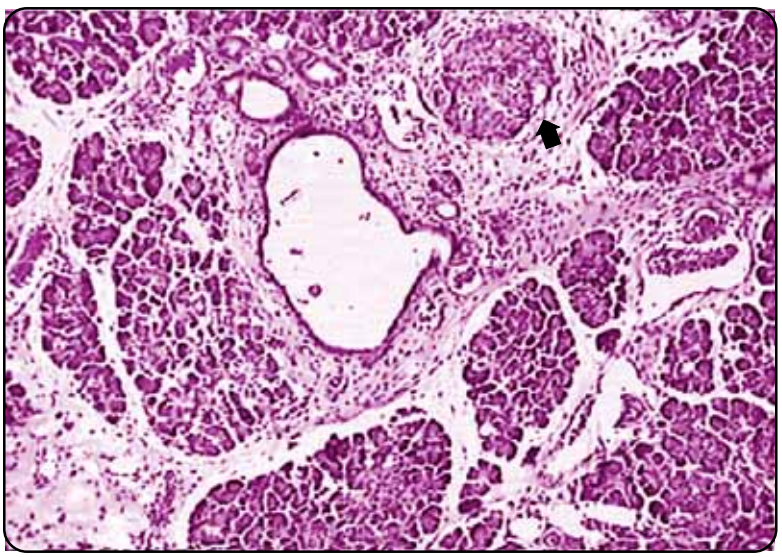
4. Disrupted lobule. There is no inflammation or fibrosis. An intercalated duct can be seen in the lower part among the acinar cells showing nuclear activity. (arrow)



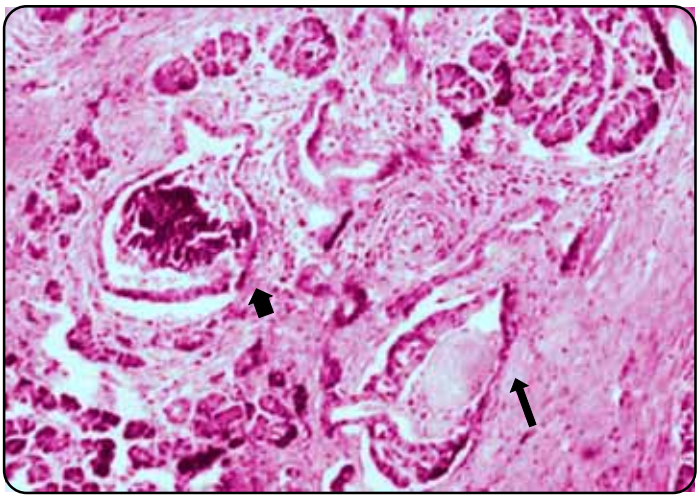
5. Extreme atrophy and acinar morphological 'obsolescence'. The isolated cells are represented by naked nuclei.



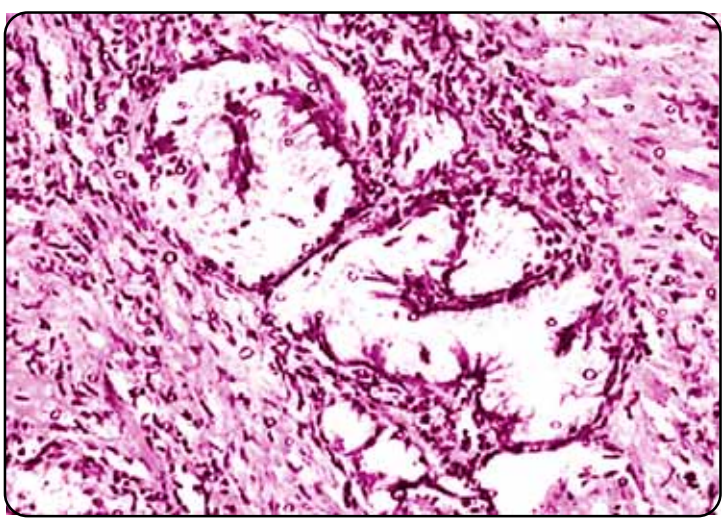
6. 'Cirrhosis' of the pancreas. Calculi, from the dilated duct has been removed. A regenerated islet is seen at the top right of the field. Interlobar fibrosis and lymphocytic infiltration can be seen.



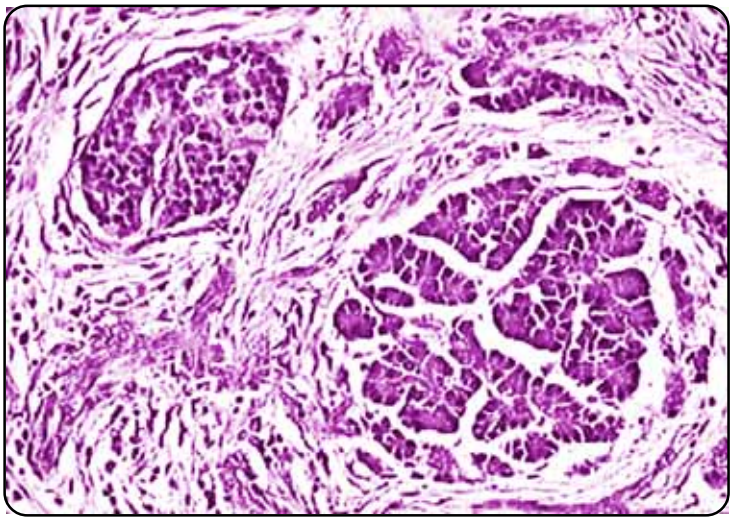
7. Exocrine pancreatic atrophy, mucus plug in the dilated duct (long arrow) and calculi (short arrow) can be seen in the duct. The ductal epithelium is metaplastic and stratified. Inflammation is minimal.



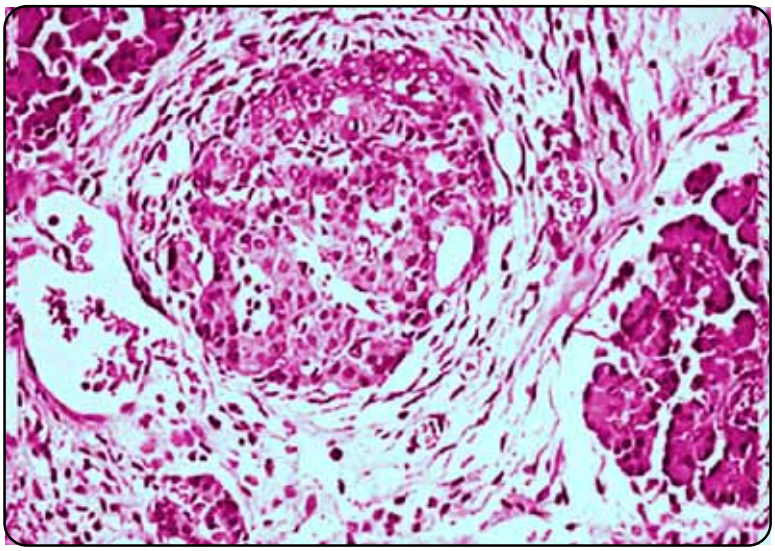
8. Advanced mucinous metaplasia of the ducts.



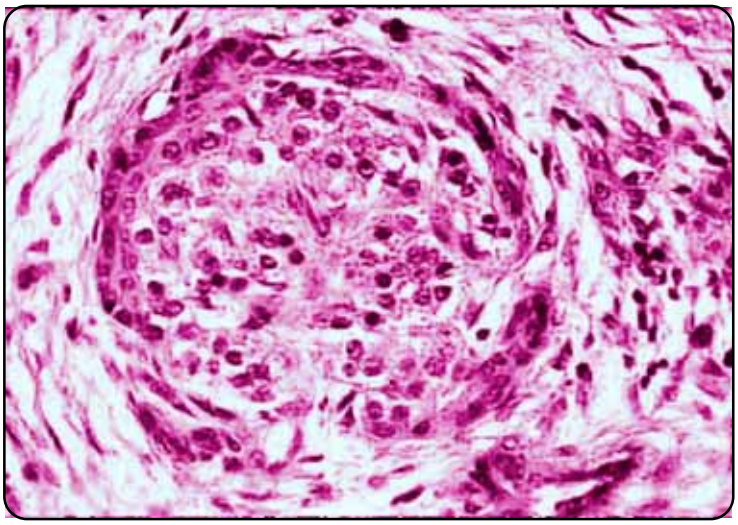
9. Exocrine atrophy, and a large regenerated islet, nearly as big as the atrophic lobule can be seen.



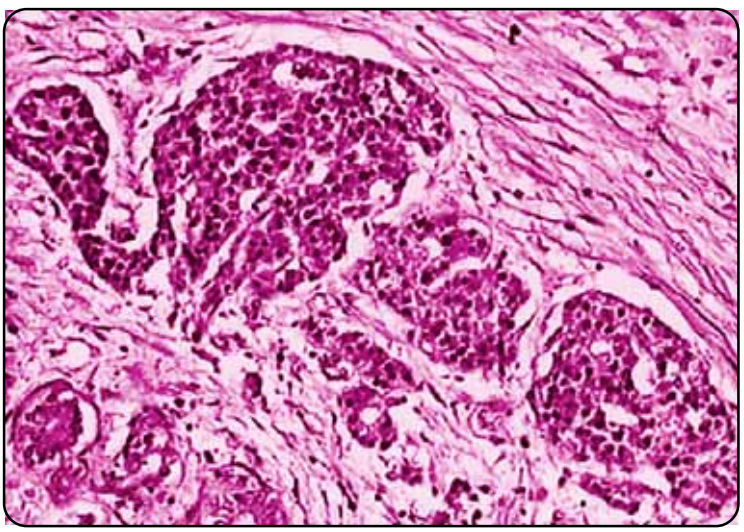
10. Nesidioblastosis. The cells at the top, forming part of the ductal linings, have proliferated and differentiated into endocrine cells.



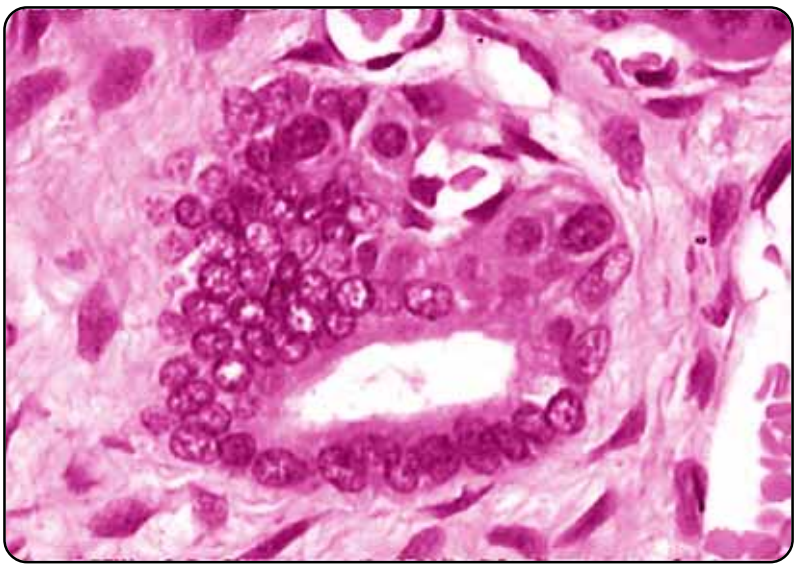
11. Nesidioblastosis. The duct of origin is seen at the top of the islet.



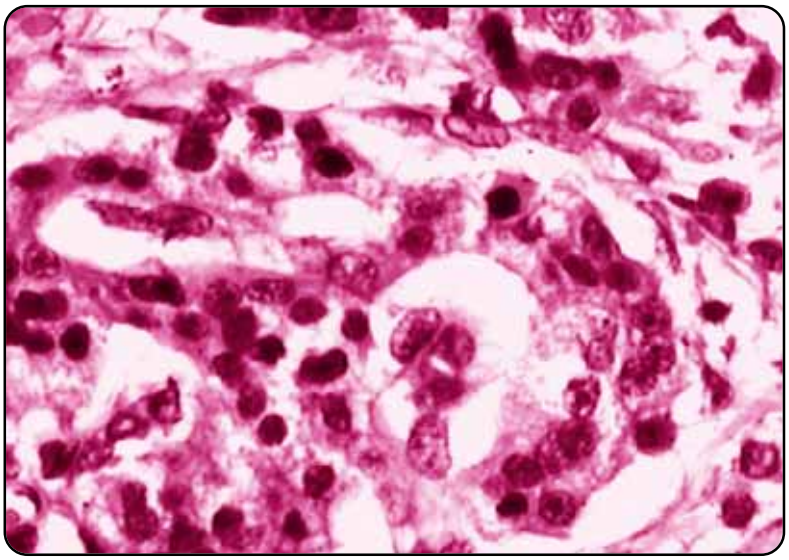
12. A bunch of regenerated islets. They are of all sizes and shapes in comparison with the normal islets which are usually small and round.



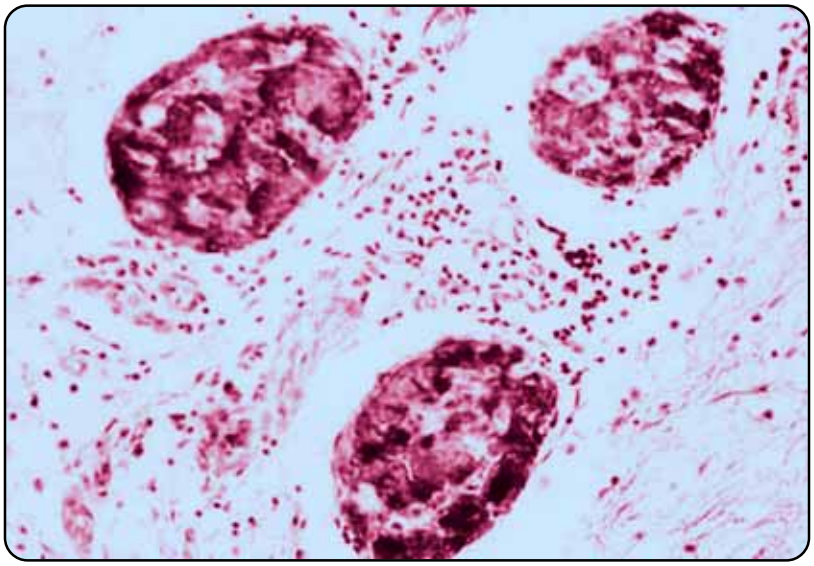
13. Active nesidioblastosis from ducts.



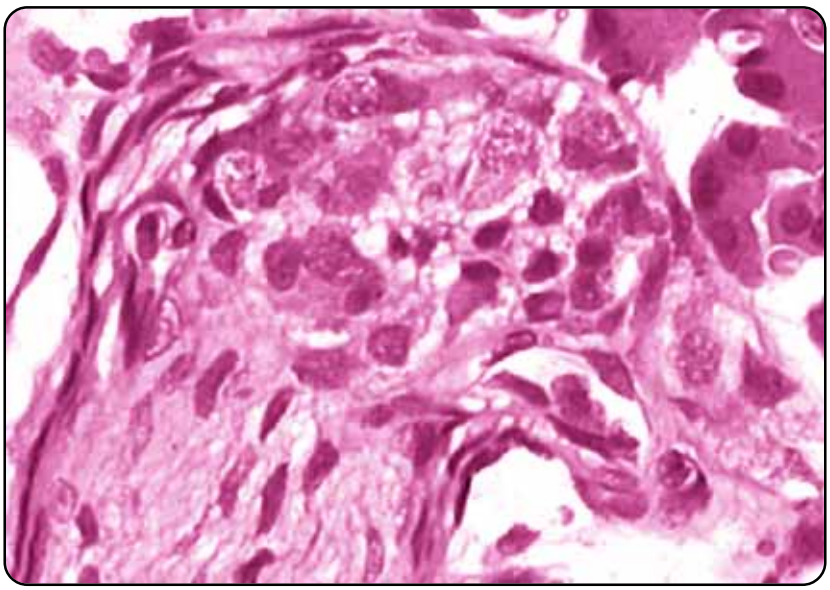
14. Islets regenerated from ducts.



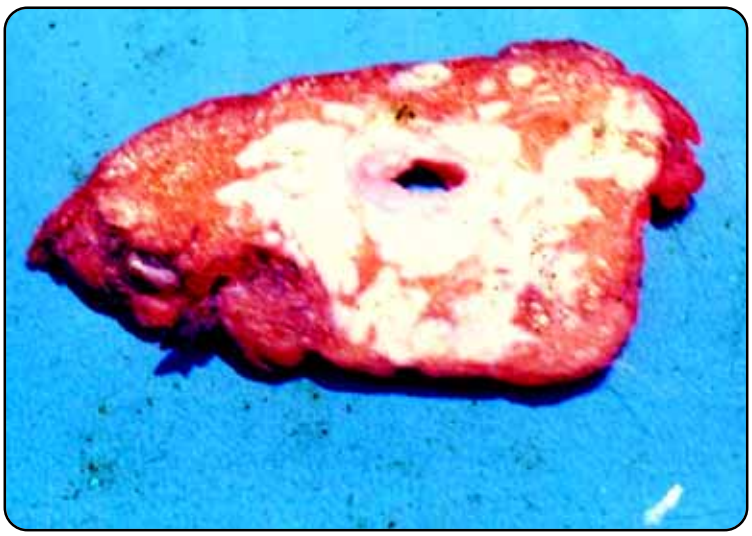
15. Insulin production by the regenerated islets, the islets are rich in β-cells. (IHC)



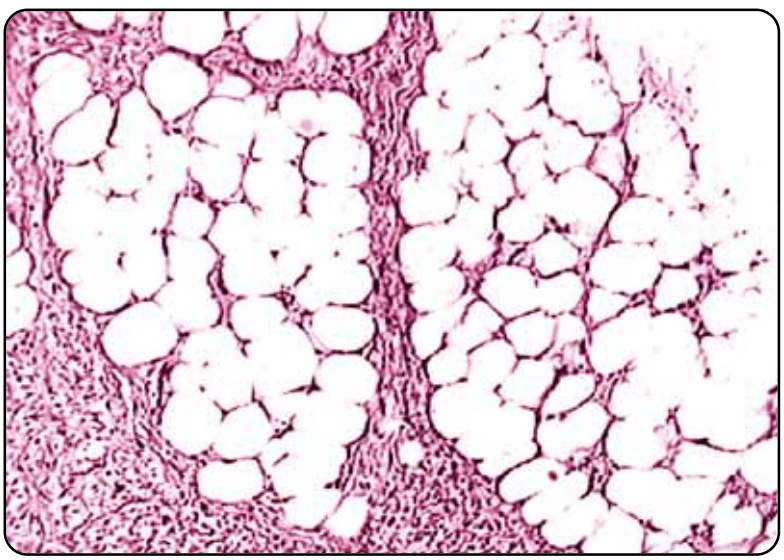
16. Neuroendocrine cells at the tip of a nerve seen in CCP. Prominent nerves and ganglion cells are common in CCP.



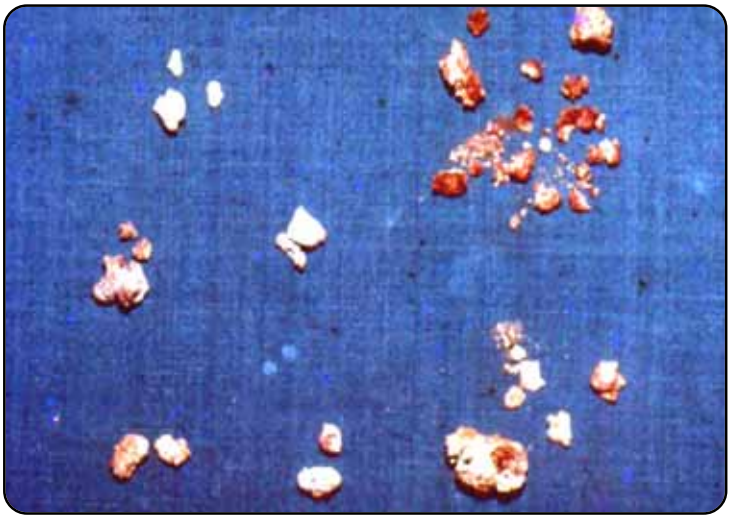
17. Lipomatous atrophy of the pancreas. Transverse section of pancreas stained with Sudan IV. The red areas indicate fat. The white areas show the surviving pancreatic tissue.



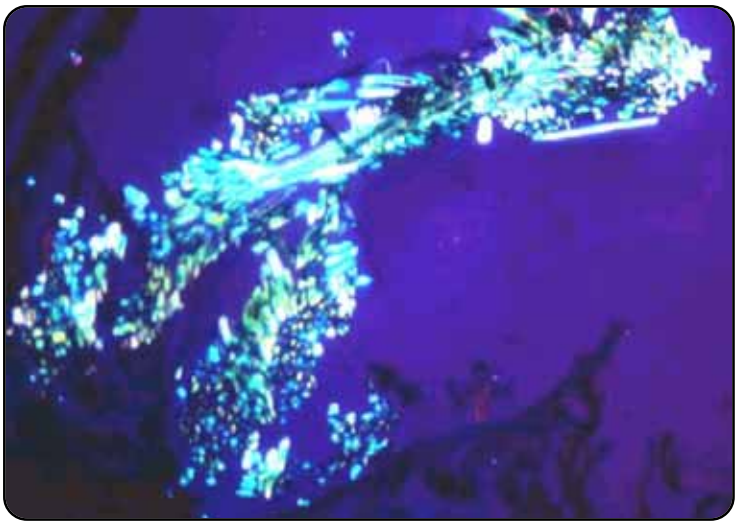
18. Lipomatous atrophy of pancreas showing only fat and fibrous tissue. No exocrine or endocrine tissue is seen.



19. Pancreatic calculi from a case of CCP. They differ in size, shape varying from gravel size to large, smooth, facetted and coralloid ones.



20. Energy dispersive x-ray fluoresence photomicrograph of a stag-horn calculus. (courtesy Dr. C.S.Pitchumoni). Helps in elemental analysis.



References

1. Augustine.P and Ramesh.H, Is Tropical Pancreatitis Premalignant? American journal of Gastroenterology, 1992; 87:1005.
2. Balakrishnan.V. Tropical Pancreatitis. Epidemiology, Pathogenesis and Aetiology in Chronic Pancreatitis in India. Indian Society of Pancreatology.1987: 81-82.
3. Brown.R.E,Madga.G.E,Cystic Fibrosis and Nesidioblastosis Arch Path.1971;92:53-57.
4. Bartow.S.A.Mukai K,Rosaij.Pseudo neoplastic Proliferation of Endocrine Cells in Pancreatic Fibrosis.Cancer 1981;47:2627-2633.
5. Bowels,Kloppel.G.Islets neogenesis in the Pancreas Virchows Arch,1996;42:553-560.
6. Bockman.D.E,Black.O,Jr,MillsJR,Webster.P.D,Origin of tubular complexes during Induction of Pancreatic Adenocarcinoma by 7,12-di methylbenzanthracine. AmJ.Pathol.1978;90:645-665
7. Bockman.d.E,Boydson.w.R,Anderson.W.C,Origin of Tubular complexes in human chronic pancreatitis.Am J.Sur 1982;144:243-249.
8. Chari.S.T,Mohan.V,Pitchumoni.C.S,Vishwanathan.N,Madanagopalan. N,Lowenfels. A.B.Risk of Pancreatic carcinoma in Tropical Calcified Pancreatitis; An epidemiological Study. Pancreas 1994;9:62-66.
9. Geeverghese.P.J.Pancreatic Diabetes.Bombay Popular Prakasahan.1968.
10. Geeverghese.P.J,Calcific Pancreatitis.St.Joseph's Press, Trivandrum.1986.
11. Chari S T, Mohan.V, Jayanthi, Snehalatha.C, Malathi.S, Vishwanathan.A and Madanagopalan.N.Comparative study of the Clinical Profiles Of Alcoholic Chronic Pancreatitis and Tropical Chronic Pancreatitis in Tamilnadu (SI). 1992; I 7: 52-58.
12. Chiakki Odaira, Regine Choux, Mary jose Payan, Dale.E.Bockman and Henri Sarles, Chronic Obstructive Pancreatitis, Nesidioblastosis, and small endocrine Pancreatic tumor, July1987; 32: 770-774.
13. Damal.C.Mathangi, Raj Deepa, Vishwanathan Mohan, Meera Govindarajan and Ambalavanan Namah Sivayam.Long Term ingestion of Cassava (tapioca) Does Not Produce Diabetes Or Pancreatitis In the Rat Model, International Journal of Pancreatology.june2000; 27: 203-208.kjkj
14. Friedlander.E.O.Hyperinsulinism Secondary to disease of the pancreas and organs adjacent to pancreas.A review of World Literature,AmJ Int Med.1960;52:838-848.
15. Henri Sarles and Jose Sahel, pathology of Chronic Calcifying Pancreatitis, American Journal of Gastroenterology, Aug1976; 66: 117.
16. Henri Sarles, Chronic Calcifying pancreatitis-Chronic Alcoholic Pancreatitis, AJG, 1974; 66: 604-616.

17. In-Sun Park and Moise Bendayan, Characterization of the Endocrine Cells in the Pancreatic Bile Duct System of The Rat, 1992; 247-255.

18. Isaksson.G,Ihse.I,Lundquisy.I.Influence of pancreatic duct ligation on Endocrine and exocrine rat pancreas.Acta.Physiol.Scand.1983;117:281-285.

19. Kazuhiro Mizumoto, Shunji Kitazawa, Shinichi Ito, Yoshiharu kashima, Masahiro Tsutsumi, Ayumi Denda, and Yoichi Konishi. Cycles of Repeated Augmentation Pressure in Rapid Production of Pancreatic and Cholangiocellular Carcinomas in hamsters Initiated with N-Nitrosobis (2-oxopropyl) amine.Carcinogenesis.1989; 10: 1457-1459.

20. Kazuhiro Mizumoto, Shinchi Ito, Shunji Kitazawa, Masahiro Tsutsumi. Ayumi Denda and Yoichi Konishi.Inhibitory Effect of Butilated Hydroxyl anisole Administration on Pancreatic Carcinogenesis in Syrian Hamsters Initiated with N-nitrosobis- (2-oxopropyl) amine.Carcinogenesis.1989; 10: 1491-1494.

21. Kazuhiro Mizumoto, Takehiko Inagaki, Masaki Koizumi, MasatoUemura, Masaaki Ogawa, Shunji Kitazawa, Masahiro Tsutsumi, Motokuni toyokawa and yoichi Konishi.Early Pancreatic duct Adenocarcinoma. 13 July 1987;. 242-244.

22. Kazuhiro Mizumoto, Masahiro Tsutsumi, Ayumi Denda, Yoichi Konishi.Rapid Production of Pancreatic Carcinoma by Initiation with N-Nitroso-dis (2-Oxopropyl) amino and Repeated Augmentation Pressure in Hamsters. Journal Of The National Cancer Institute.1988; 80.

23. Kazuhiro Mizumoto, Masahiro Tsutsumi, Shunji Kitazawa, Shignobu Tsujita, Masaki Nakayama, Tadasu Tsujii, Hiromichi Kanehiro, Yoshiyuki Nakajima, Hiroshige Nakano and Yoichi Konishi.Intraductal Carcinoma In a Surgically Resected Pancreas with Chronic Pancreatitis. Int: Journal Of Pancreatology. 1989: 279- 284.

24. Knud C. Stobbe, William H. Remine, and Archie H. Baggenstoss.Pancreatic Lithiasis. From sections of surgery& experimental & Anatomic Pathology. 1090-1098.

25. Laidlaw.G.F. Nesidioblastoma,the Islet Cell Tumor Of Pancreas. AmJ.Pathol. 1938:XIV:125-134.

26. Laszik,Pap.A,Farkas.G,Ormos.J.Endocrine Pancreas in Chronic Pancreatitis.A Qualitative and Quantitative study.Arch Pathol Lab Med.1989;113:47-51

27. Lawrence Rosenberg, Ronit Rafaeloff, David Clas, Yoichiro Kakugawa, Gary Pittenger, Arthur I. Vinik, and William P. Duguid. I

28. Induction of Islet Cell Differentiation and New Islet Formation in the Hamster – Further Support for a Ductal Origin. Pancreas. 1996; 13: 38-46.

29. Lelio Orci, Bernard Thorens, Mariella Ravazzola, Harvey F. Lodish.Localization of the Pancreatic Beta Cell Glucose Transporter to Specific Plasma Membrane Domains. 245. July 1989: 295- 309.

30. Little.J.M,Lauer.C,Hogg.J.Pancreatic duct Obstruction With Acrylate Glue.a new method for producing pancreatic exocrine atrophy,Surgery1977;81:243-245.

31. Masaharu Matsuzaki, Tsuneo Natori, Kazuhiro Mizumoto, Shunji Kitazawa, Masahiro Tsutsumi, and Yoichi Konishi. Intracellular Distribution of Pancreatic tumor Antigen Purified from BHP- Induced Adenocarcinomas in Syrian Hamsters. Pancreas. 1989; 4: 429-435.

32. Masahiro Tsutsumi, Yoshinori Murakami, Satoshi Kondoh, Toshifumi Tsujiuchi, Kanya Hohnoki, Kohsuke Horiguchi, Osamu Noguchi, Eisaku Kobayashi, Shunji Okita, Takao Sekiya and Yoichi Konishi. Comparison of K-ras Ocogene Activation in Pancreatic Duct Carcinomas and Cholangiocarcinomas Induced in Hamsters by N- Nitrosobis (2-hydroxypropyl) amine. Jpn.J.Cancer Res. 84. Sept 1993; 956-960.

33. Masahiro Tsutsumi, Toshifumi Tsujiuchi, Satoshi Kondoh, Toshihiro Amanuma, Kohsuke Horiguchi, Kazumi Shiraiwa, Kazuhiro Mizumoto, Kazutoshi Tamura, Hiroshi Maruyama, and Yoichi Konishi. Lack of effects of Cholecystokinin and Proglumide, Antagonist of its Recepter, on Pancreatic Ductal Carcinogenesis Induced by N- Nitrosobis (2-Hydroxypropyl) amine in Hamsters. Journal of toxicologic Pathology 5. 1992: 89-194.

34. Mizumoto K, Tsutsumi M., Kitazawa S, Denda A, and Y. Konishi.Usefulness of Rapid Production Model for Pancreatic Carcinoma in Male Hamsters. Cancer Letters, 1990; 49: 211- 215.

35. Moise Bendayan. Anatomic Basis of Islet – Acinar Interaction in the Pancreas. A Quarterly Clinical Review. 2: 3, 1990: 1-15.

36. Mohan V, Premalatha G. Fibrocalculous pancreatic Diabetes. Int J. Diabetes. 1995: 71-82.

37. Mohan.V, Snehalatha.C, Jayashree et al.Pancreatic B-cell function Tropical Pancreatic Diabetes.Metabolism1983;32:1091-1092.

38. Mohan.V, Snehalatha.C,Ramachandran et al.Plasma Glucagon responses in Tropical Fibrocalculus Pancreatic Diabetes. Diabetes Research and Clin. Pract. 1990; 9:97-101.

39. Mohan.V,Chari.S.T,Vishwanathanet al,Tropical Calcific Pancreatitis In Southern India.Proc.Roy.College of Phy 1990;20:34-32.

40. Montalto. In Vitro Function of Human Islets Isolated from the Pancreas of a Cadaveric Donor with Diabetes Mellitus Secondary to chronic Pancreatitis. Pancreas. 1994; 9: 134- 138.

41. Nagalotimath.S.J.Pancreatitis in Karnataka.A Note on Pathology of Chronic Pancretitis in India.Ed.Balakriushnan.Indian Society of Pancreatology.St.Joseph's 1987;107-111.

42. Nair B and Latha T. Pancreas in chronic calcific pancreatitis. Chronic pancreatitis in India. Ed.V.Balakrishnan. Trivandrum. Indian Society of Pancreatology. 1986:115-120.

43. Nicole M. Le Douarin. On the Origin of Pancreatic Endocrine cells. 1988; 53: 169-171.

44. E. O. Olurin, Oyinade Olurin. Pancreatic calcification. British medical Journal. 1969: 534 –538.

45. Oliver Fitzgerald, Patrick Fitzgerald, James Fennelly, Joseph P. McMullin, and Sylvester J. Boland. A. Clinical Study of Chronic Pancreatitis. Gut, 1963;4:193-215.

46. Parviz Pour. Islet cells as a Component of Pancreatic Ductal Neoplasms.American Journal of Pathology. 295-306.

47. Pearse A.G.E. Islet development and the Apud Concept. Pancreatic Pathology. 125-130.

48. Pitchumoni C. S. and Orlando Bordalo. Evaluation of Hypothesis on Pathogenesis of Alcoholic Pancreatitis. American Journal of Gastroenterology. 1996;91:637-647.

49. 51. Pitchumoni C. S. Role of Nutrition in Chronic Pancreatitis Div: of

50. Gastroenterology& Clinical Nutrition.15-25

51. Pitchmoni.C.S.Special Problems in Tropical Pancreatitis.Clin Gastroenterology.1984;13:941-951.

52. Rajan N. Anandakumar M, Abdul Kalam, Balakrishnan. V. Surgery for Chronic Pancreatitis. Kerala Surgical Journal. 1995;2:7-14.

53. Ren.C.L., Sharer.N, Schwartz, Cohn J.A., Silverman L.M., Knowles M.R.

54. Mutations of cystic fibrosis gene in Pancreatitis N.Engl.J.Med.99;40:38-239

55. Rosenberg.L and A. I. Vinik. Induction of Endocrine Cell Differentiation: A New Approach to Management of Diabetes. Pancreatic Endocrine Cell Differentiation. 75-83

56. Rosenberg.L,Duguid.W.T,Brown.R.A,Vinik.A.I.Induction of Nesidioblastosis will reverse Diabetes in Syrian golden hamster.Diabetes 1988;37:334-341.

57. Rosenberg L, W P Duguid, and A. I. Vinik. The Effect of Cellophane

58. Wrapping of the Pancreas in the Syrian Goldern Hamster: Auto

59. Radiographic Observations. Pancreas , 1989;4 :37.

60. Rosenberg.L,Rafaeloff.R,Clas.D et al,Induction of Islet Cell Differentiation and new Islet cell formation in hamster-further support for

ductular origin. Pancreas 1996;13:38-46.

61. Samal K. C. PDDM: Fact or Fiction. Medicine Update.1992; 2: 89-93.

62. Sandhyamoni S. and Balaraman Nair. Pancreas in Induced Malnutrition. Bonnet Monkey Models for Pancreatic changes in Protein Malnutrition& Tropical Chronic Calculus Pancreatopathy.

63. Sarles.H,Chronic Calcifying Pancreatitis-Chronic Alcoholic Pancreatitis.Gastroenterology1974;66:604-616.

64. Sarles.H.Pathology of Chronic Calcifying Pancreatitis. AmJ. gastroenter. 1976; 66.

65. Sherwood Githens, The Pancreatic Duct Cell: Proliferative Capabilities, Specific Characteristics, Metaplasia, Isolation, and Culture. Journal of pediatric gastroenterology and nutrition, 1988; 7: 486-506.

66. Ramachandran.A, Roosenbloom.A.L, Mohan.V, Snehalatha.C, Vishwanathan M, Riley W.J, Maclaren N.K, Kooperman S. Autoimmunity in South Indian Patients with IDDM.1986;9

67. Timon.W.Van Haeften.Clinical Significance of Insulin Antibodies in Insulin-Treated Diabetic Patients. Diabetes Care, 1989; 12: 641-648.

68. Traverso W.L, Bockman D.E, Pleis. S.K, Dail D.H. Nesidioblastosis as a Mechanism to prevent Fibrosis–Induced Diabetes after pancreatic Duct obstruction.pancreas1993;8:325-329.

69. Simmy Bank, I.N. Marksand Vinik A.I. Clinical and Hormonal Aspects of Pancreatic Diabetes. AJG 1975; 64:13-22.

70. Sridhar G.R. Malnutrition Related Diabetes Mellitus. JAPI 1994;42: 561-564.

71. Sue A. Bartow, Kiyoshi Mukai, and Juan Rosai. Pseudoneoplastic Proliferation of Endocrine Cells in Pancreatic Fibrosis. Cancer 1981; 47: 2627-2633.

72. Tatsuo Tomita, James Rhodes, John Falscroft, Vera Doull, Joe.R.Kimmel, and Gail Pollock.H. Endocrine Pancreas in the Rat Model of Exocrine Pancreatic Insufficiency. Pancreas 1988 ; 3: 568-575.

73. Toshifumi Tsujiuchi, Masahiro Tsutsumi, Ayumi Denda, Toshihiro Amanuma, Satoshi Kondoh, Kenji Kamino and Yoichi Konishi.Effects of 3-Amino Benzamide on Induction of Multiorgan Carcinogenesis by N-Nitrosobis (2-hydroxypropyl) amine in Hamsters.Jpn.j.cancer July1991; 86: 793-799.

74. Toshihiro Amnuma, Kazuhiro Mizumoto, Masahiro Tsutsumi, Toshifumi Tsujiuchi, Shunji Kitazawa, Kiyohiko Hasegawa, Ayumi Denda, Hiroshi Maruyama and Yoichi Konishi. Initiating Activity of Diehtynotrisamine in a Rapid Production Model for Pancreatic Carcinomas in Syria Hamsters.Jpn.J.Cancer Res.June 1991; 82: 632-637.

75. Toshihiro Amanuma, Ayumi Denda, Mashiro Tsutsumi, Toshifumi Tsujiuchi, Satoshi Kondoh, Kazutoshi Tamura, Hiroshi Maruyama, and Yoichi Konishi.Evaluation of Combination Effects of Three Carcinogens at Low Dose: Initiation of Pancreatic Ductal Carcinogenesis in a Syrian Hamster Rapid Production Model.J.Toxicol.Pathol 1991; 4: 45-152.

76. Toshiki Kamano, Junji Tamura, Takayuki Uchida, Tsutomu Kanno, Noburu Sakakibara, Masahiro Tsutsumi, Hitoshi Maruyama AND Yoichi Konishi.Studies by Pancreatography of Ductal Changes Induced by Administration of Pancreatic Carcinogen in Two Dogs.Jpn.J Clin Onco 1991; 21: 282-286.

77. Tripathy B.B. and Samal.K.C.Protein Deficient Diabetes Mellitus in India. Int.J.Diab.Dev.Countries 1993;13: 3-13.

78. Tsujiuchi.T, Mizumoto.K, Tsutsumi.M, A.Denda, T.Amanuma, S.Kondoh and Y.Konishi.Effets of 3-aminobenzamide on the Post-Initiation Phase of N-nitrosobis (2-oxopropyl) amine Induced Pancreatic Carcinogenesis in Syrian Hamsters. Cancer Letters 1991; 61: 61-66.

79. William.L.Traverso, Dale E.Bockman, S.K.Plies, and David.H.Dail. Nesidioblastosis as a Mechanism to Prevent Fibrosis-Induced Diabetes After Pancreatic Duct Obstruction. Pancreas 1993; 8: 325-329.

80. Yajnik.C.S, Shelgikar,Sahasrabudhe et al.The Spectrum of Pancreatic Exocrine and Endocrine(b-cell)Function in Tropical Calcific Pancreatitis. diabetologia 1990;33:417-421.

81. Yoichi Konishi, Kazuhiro Mizumoto, Shunji Kitazawa, Toshifumi Tsujiuchi, Masahiro Tsutsumi, and Toshiki Kamano. Early Ductal Lesions of Pancreatic Carcinogenesis in Animals and Humans. Int.J.Pancreatology 1990: 83-89.

Chapter 21

Fibrocalculous pancreatopathy

Nagalotimath SJ

Summary

Fibrocalculous Pancreatopathy is an enigmatic disease. In this article, I discuss my experience with examining the histological spectrum of these cases, over several decades. In some cases, especially the advanced stages of the disease, the pathology is quite characteristic. However, in a proportion of cases, the disease process seems to have reached a static phase, or a phase of arrest. These cases of arrested disease need to be studied in detail as they could provide interesting insights into the pathogenetic factors involved in the disease, and thereby offer new therapeutic targets for studying the illness.

Introduction

Fibrocalculous pancreatopathy was known earlier as fibrocalculous pancreatic diabetes (FCPD). As the name points out this is a type of diabetes where there is significant fibrosis of the parenchyma of pancreas and in addition, the ductal system reveals calculi. The term fibrocalculous pancreatic diabetes is preferred to fibrocalcific pancreatic diabetes, for this is an illness that is not associated with tissue calcification. This disorder has been noted in other developing countries. In India the disorder initially appeared to be almost restricted to southern parts.

Clinically these cases first present below the age of 30 years. Many of them present during the first decade of their life with recurrent attacks of abdominal pain and symptoms pointing to diabetes mellitus. The patients are poorly built and nourished with other features of malnutrition. The patient's blood examination shows moderate to severe hyperglycemia and usually requires insulin for control. Ketosis may or may not be present. There will be some amount of 'C' peptide secreted by the gland.

Radiographic demonstration of calculi in the ductal system of pancreas will confirm the diagnosis. Presence of stones in the pancreas can also be confirmed by ultrasonography. There seems to be two stages of this disorder. One is identified as " advanced" stage, while the other one is called " arrested". Cases of advanced disease will have classical symptoms and they will die of complications of diabetes. Cases of arrested diseases

will not manifest with diabetes and may die of some other disease. Subjects with arrested disease are detected accidentally by radiologists or by pathologists in autopsy room.

Gross Pathology

Several workers have studied and described the features of the organ in this disorder. Pancreas is markedly shrunken in size, shape is distorted. The normal lobular appearance is lost. The capsule is thickened and opaque. Hence, the organ looks like a sac or bladder. There are no adhesions to the surrounding tissues and the consistency varies from cystic to hard. The tissue is tough to cut. Unopened specimens when examined radiologically show multiple stones in the ducts. Some of the specimens show radio-opacity of the mucoid material in addition to the stones. The duct can be probed easily through ampulla of Vater. On opening the organ along with the main duct one finds markedly dilated ducts and ductules. The parenchyma is reduced to a capsule-like structure. The ducts and ductules are filled with abnormal mucoid secretions. This material is thick and viscid. It may be transparent like mucus or could be cloudy. Stones are usually submerged in this mucoid material. There are no strictures. There is no area where the stones are blocking the lumen tightly. The dilatation is marked. At times, ducts show cystic dilatations. Ductal surface is smooth, shiny and free from any projections. At places the surface looks like parchment paper. At no point do the ducts show thickening of their walls. The stones vary in size. They could be as small as sand granules or as big as two centimeters in their length. Most of the stones have the configuration of the ducts. But they are not impacted. They are cylindrical or oval. Their ends are blunt. Occasionally the ends are faceted. Surface of stones could be granular, sticky or smooth. Some stones are light and moldable. They could be termed " putty stones". The color also varies. Some are dirty white and others chalky white.

Microscopy

Microscopic examination reveals extensive fibrosis. Fibrosis is universal and not limited to one zone or area. It is intra and inter lobular. There is no periductal fibrosis, capsule is thickened. Small islands of parenchyma

are noted in fibrous bands. Fibrous tissue irregularly dissects the surviving lobules. The acini are markedly reduced in number. Wherever they are seen, they show some pink secretory material in the lumen. The acinar cells look smaller in size. The intercalated ducts show mild dilation with pink secretion. The intra lobular and inter lobular ducts are also less in number but dilated. They are bundled together to form clusters giving an apparent look of ductal proliferation. The lining epithelium of the ducts shows goblet cell metaplasia. The larger ducts in contact with stones show squamous cell metaplasia. The lumen of the ducts show inspissated, lamellated secretory material. At many places these mucoid plugs show layers of calcification. Acute or chronic inflammatory cells may be found in the mucoid secretions. The inflammatory cells are seen in the walls of the ducts in the periductal and parenchymatous areas. Lining epithelium may be denuded.

Islets of Langerhans are very distinctly seen in the background of sparse acini and ducts. Islets are found even in the hyalinised fibrous bands. At places they are almost strangulated. In some areas they are found in clusters of 10 to 20 islets. This seems almost like aggregation of portal triads in cirrhosis of liver. The cells in the islets look normal in size and appearance. The normal proportion of beta and alpha cells is also maintained. Nesidioblastosis is found much reduced. In short, total insular mass is decreased. No specific inflammation of islets to be identified as insulitis is noted.

Previously inflammation of pancreas was suspected. These observations made were on totally burnt out cases. However, Geeverghese had observed inflammation in the pancreas. As the workers studied the organs of patients in the early phases of disease, they confirmed the existence of inflammation. The inflammation noted in the organ is more a reaction to the damage done to pancreas. Therefore, one should not draw a conclusion of inflammation as a precipitating cause of this disease. Inflammation in this disorder comes at the time of the end-stage destruction of the pancreas and not at the beginning of the lesion.

The inflammatory cells are of mixed cellular type. Moreover, lymphocytes and plasma cells predominate. Occasionally lymphocytes are found forming germinal centers. Some nerve bundles are seen surrounded by

lymphocytes. Fibrous bands are also studded with lymphocytes. Inflammatory cells are noted in the lumen of ducts. In this disorder, only lithiasis is evident in the ducts and never parenchymal calcification. Similarly there is one more statement in the WHO report describing " Periductal" fibrosis. This again is to be corrected. In this disorder some how periductal fibrosis is minimal or absent. Therefore, the ducts are so much stretched and sac like or cystic. The fibrosis noted in this entity appears more in the parenchyma. Before venturing to explain pathogenesis it is necessary to understand the physiological facts about pancreatic exocrine secretions. Acinar cells secrete the enzymes in the form of zymogen granules. The granules are released into the lumen of the acini. This secretion, rich in enzymes, is viscid and slightly acidic. The flow of this material is very slow in the acini and also in the ducts. There is no peristalsis in the pancreatic ducts. The reason for absence of peristalsis is that there are no muscles in the wall of the ducts. Normally the secretion of exocrine part of pancreas should flow into the duodenum. For this, nature has designed a flushing system.

The epithelial cells of intercalated ducts and ductules are known to secrete very thin watery fluid, which is alkaline in reaction. The rate of secretion of this fluid is so fast that it can be called as a jet of fluid. This watery secretion is jetted into the lumen of acini and tubules. As a result, the viscid material gets diluted and easily flows into the main duct and finally into the lumen of the duodenum. This fluid is rich in calcium and contains a protein, identified by Sarles and Bernard. This protein is named as ' Lithostathine S' and keeps the calcium in soluble state in the pancreatic juice. Whenever there is lack of lithostatine, calcium will get precipitated. Furthermore, if this protein is degraded to lithostathine $H_{2,}$, it becomes insoluble and becomes fibrillar material. This material is also called as pancreatic stone protein (PSP) or pancreatic fibrillar protein (PFP). On the surface of such fibrillar protein calcium gets deposited. This is the genesis of pancreatic stones. Therefore, pathogenesis of pancreatic stones is different from lithiasis elsewhere.

There are several changes related to the pancreatic juice abnormalities: flow of the juice is sluggish, stagnation and stasis sets in, the intra-luminal pressure increases and finally, there is distention and stretching up of acini, intercalated ducts, ductules and ducts.

With the knowledge of physiology and pathological findings one is inclined to think in the following lines about the probable pathogenesis of FCPD. Primary lesion appears to be in the epithelial cells of intercalated ducts and intralobular ductules. Still unknown or unidentified etiological agents act on these cells. These cells get damaged. As a result the watery alkaline secretion of these cells will be absent or reduced. The flushing out system fails. The enzymes secreted in the lumen of the acini are not drained. Pressure increases in the acini. Acinar cells stop functioning. Gradually they undergo pressure and disuse atrophy. The death of acinar cells invites inflammation and replacement fibrosis. The already secreted enzyme rich material gets pent up in the ductules and ducts. Therefore, abnormal secretory mucoid material in the lumen stretches the ducts and ductules. This secretion irritates the lining epithelium of ductal system. The result is metaplasia of ductal epithelium.

The primary injury to the ductal epithelial cells may also lead to inadequate secretion of lithostathine S protein. Whatever amount of lithostathine S is present in the secretion may get degraded to lithostatine H_2 which is insoluble in neutral or acidic pH. So this protein moiety gets precipitated in the ducts and ductules as protein casts. Marked reduction of lithostathine S automatically precipitates calcium carbonate in the pancreatic juice; thus there will be calcium precipitation on the surface of the mucoid proteinaceous casts. This gives eggshell like structure. Over this shell a coat of secretory material is formed. Again a layer of calcium carbonate precipitates.

Repetition of such a process forms lamellated stones in the lumen of the ducts. In those places where mucoid material is less abundant, calcium carbonate may continue to get precipitated without alternating layers of mucoid material. Such stones will be hard. Yellow or dirty yellow color of pancreatic stones can be due to mix up of epithelial cells. The over stretched ducts may give way at places allowing the secretory material to leak. This will be another cause of inflammation and fibrosis, in the intra and! interlobular places. So far the pathological changes observed in the gland could be traced out easily. Regarding the endocrine part of pancreas one can think as follows. As the inflammation and replacement fibrosis continues, acinar tissue

disappears. The existing islets of Langerhans will be left out in their places. Therefore, one may find the islets even in the fibrous bands. Disappearance of acinar tissue and contracting fibrosis seems to cluster up the islets in groups. These islets, either left out singly, or found in clusters, are surrounded by less vascular collagenised fibrous tissue. This may hinder the transport of secreted insulin to the blood circulation. Gradually deficiency of insulin is brought in. As the fibrosis continues, the diabetes becomes more and more severe. Because of disappearance of normal ductal epithelium natural processes of nesidioblastosis is hindered. Thus total insular mass is reduced.

The exocrine part will be reduced in mass. Hence, malnutrition starts manifesting. The chronic inflammation in the pancreas will explain the prominence of nerve bundles, ganglion cells, endarteritic changes, etc. This hypothesis was proposed as early as 1980 by the author. But pathogenesis of lithiasis was not explained satisfactorily. The identification of lithostathine S in normal pancreatic juice by Sarles and Bernard has given a scope to explain this aspect too. Now the etiological factor to initiate this pathology remains to be searched: nutritional deficiency, a viral infection or a toxin.

The enigma of the "arrested" FCPD

At this juncture the discussion and understanding of arrested FCPD could be meaningful. These cases are really quite interesting. Usually patients with this disorder do not suffer from diabetes mellitus. They lead a normal life. The calculi in the pancreas are detected in routine X-ray examination or they are detected at autopsy accidentally. Macroscopically the pancreas shows a segmental involvement. The segment could be in any part of the pancreas. The ducts in the involved area show mild dilatation and small stones in the lumen. The parenchyma drained by those particular tributaries is fibrosed and shrunken. That part will be firm to feel and tough to cut. No abnormal juice is found in the ducts as seen in advanced cases of FCPD. Rest of the pancreas looks totally normal. Microscopy reveals mild dilation of ducts and fibrosis of parenchyma in shrunken part. These cases of arrested FCPD appear as an incomplete answer to an unknown problem. Their occurrence in the general population suggests that certain

etiological factors act on the pancreas to precipitate FCPD. The factor or factors start acting on a part of pancreas for some time and then they are withdrawn. Rest of the pancreas continues to function normally. Hence only a small segment of pancreas is affected.

Chart 1. Probable pathogenesis and pathology of FCPD

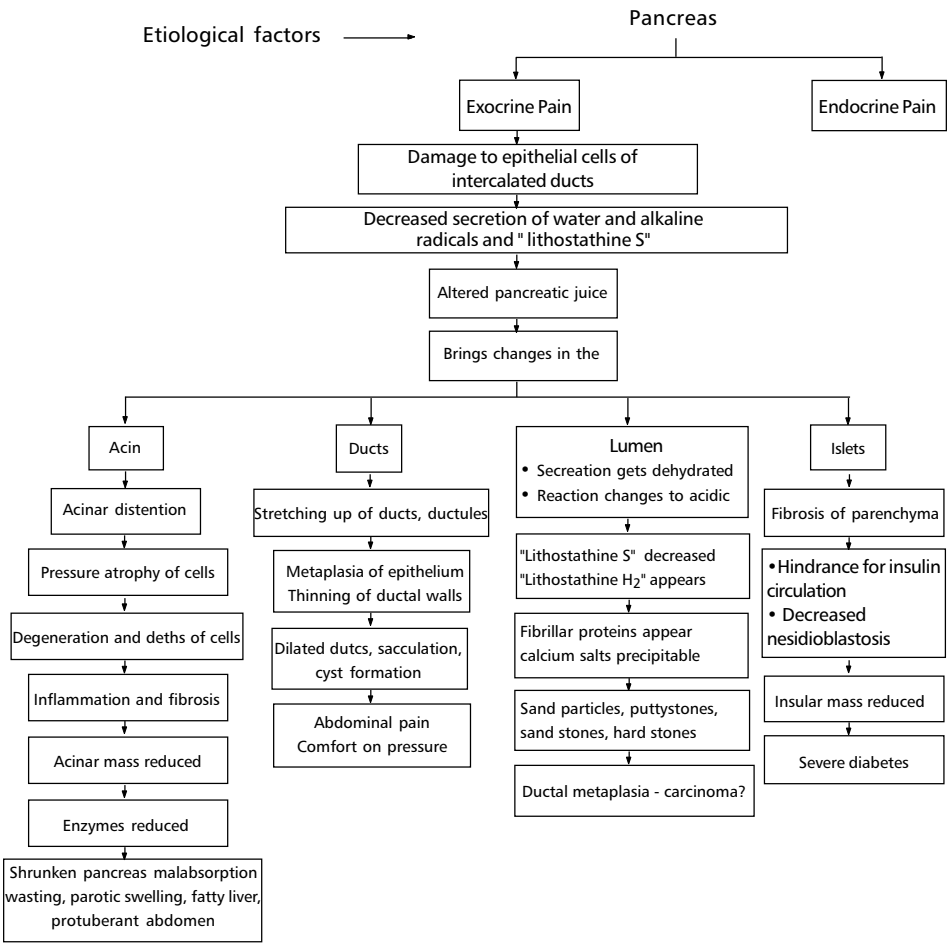


Fig. 1. Plain X-ray of upper abdomen. Note: Radio-opaque stones in the duct of pancreas.

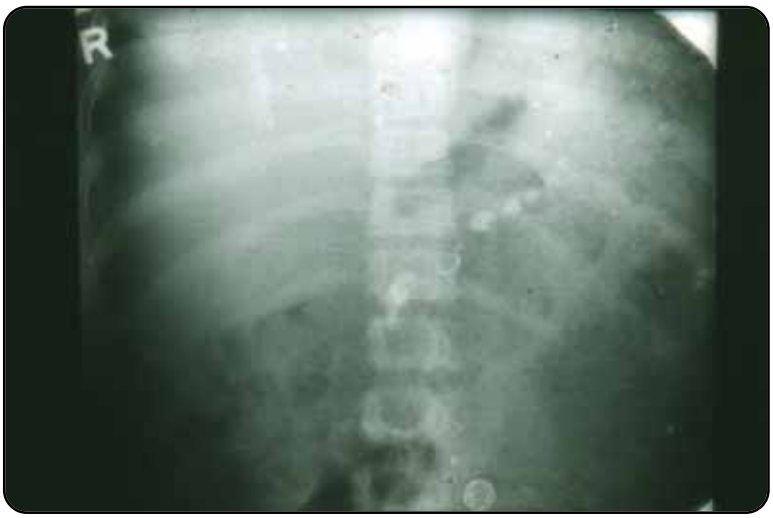


Fig. 2. Autopsy specimen of pancreas and duodenum from a case of FCPD. Note: Loss of normal lobular pattern of pancreas. The organ looks like a bladder. Few adhesions are seen. Nodularity is seen. Consistency varied from cystic to stony hard.

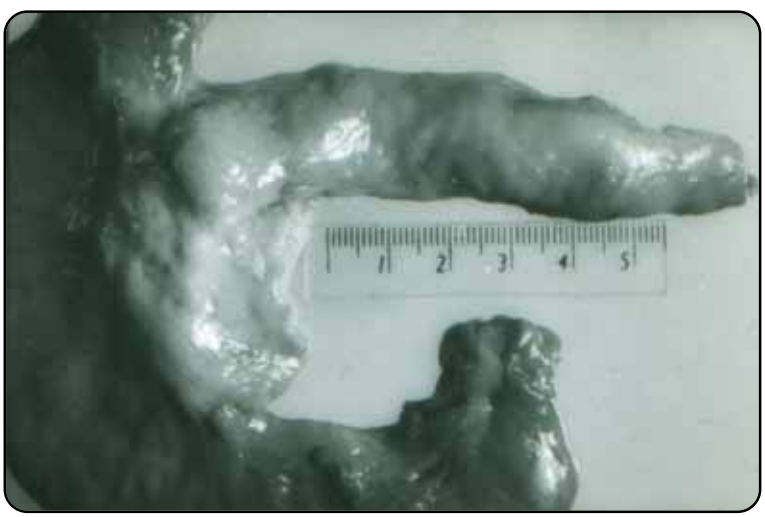


Fig. 3. Specimen of pancreas. Main duct is cut open. Large stones are seen from head to tail. Parenchyma is reduced to a flat ribbon. Main duct is markedly dilated. Opening of dilated tributaries can be seen.

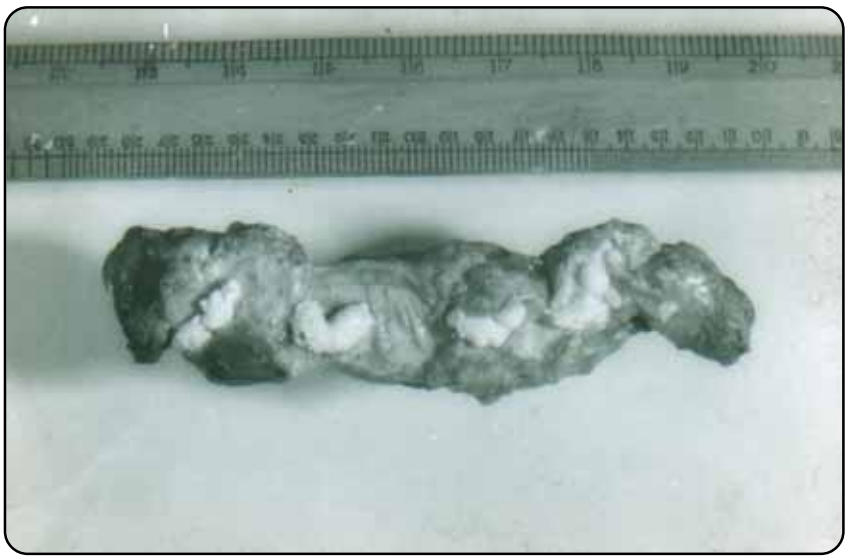


Fig. 4. Specimen of pancreas along with duodenum. Close up view. Note: normal look of ampula of Vater. Plenty of stones in the main duct.

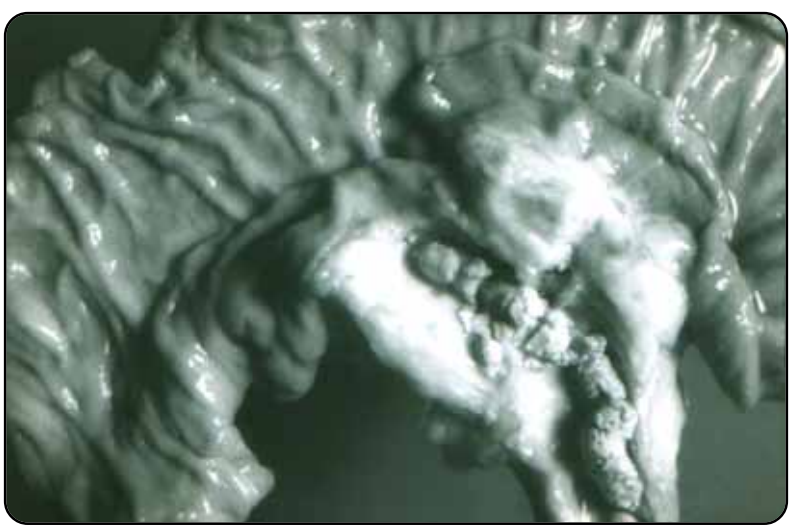


Fig. 5. Specimen of pancreas and duodenum.
Dilated duct with stones. Litmus paper is to show acidic reaction of mucus.

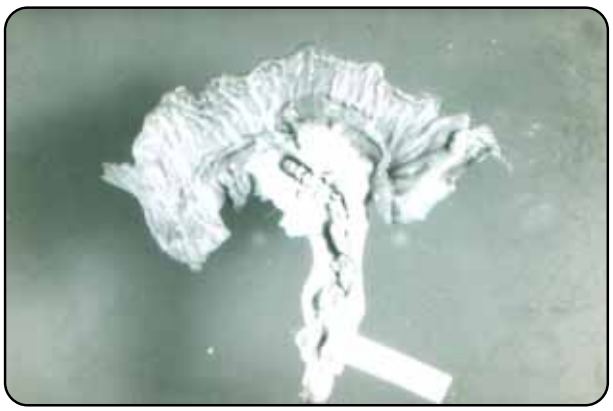


Fig. 6&7. Sections from pancreas from a case of FCPD. (H & E. 100X). Dilated duct with denuded epithelium. Lumen shows formation of microscopic stone. There are inflammatory cells.

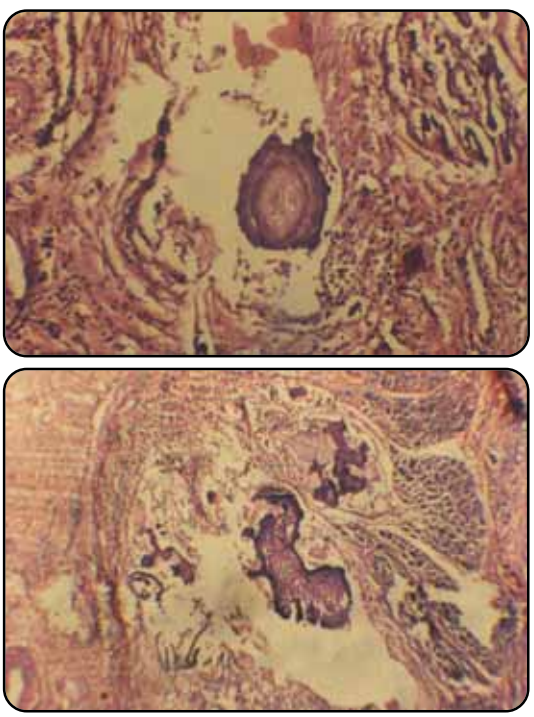


Fig. 8. Autopsy specimen of pancreas.
Dilated duct, large stones. Plenty of mucus submerging the stones. Mucous is opalescent.

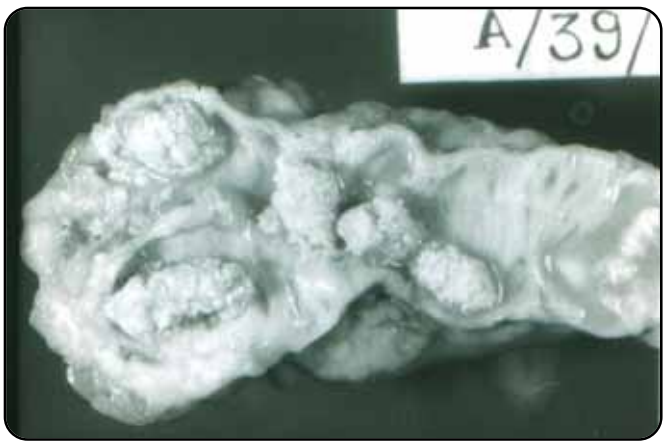


Fig. 9. Section from pancreas of a case of FCPD. (H & E - 100 X).
Tiny lobule, plenty of fibrous tissue. Dilated ducts and ductules.

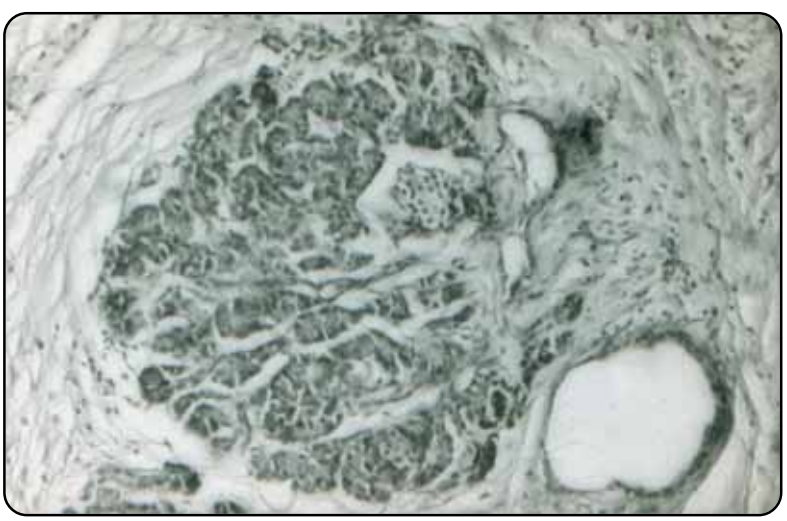


Fig. 10 & 11. Section from pancreas of a case of FCPD (H & E - 100 x) Fibrosis, aggregation of islets of Langerhans.

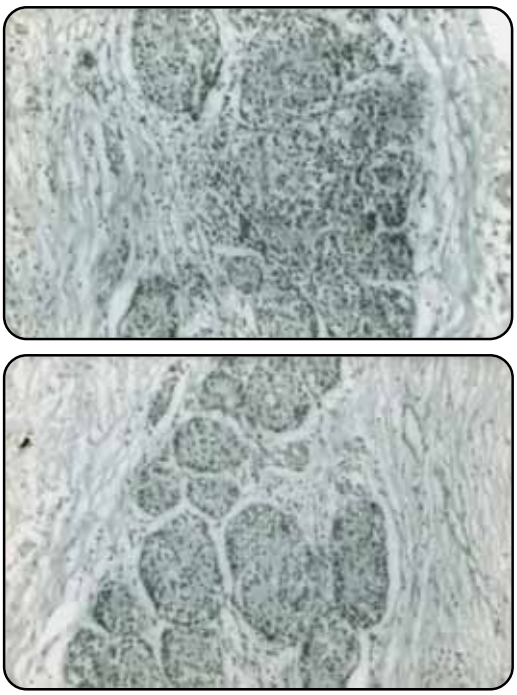
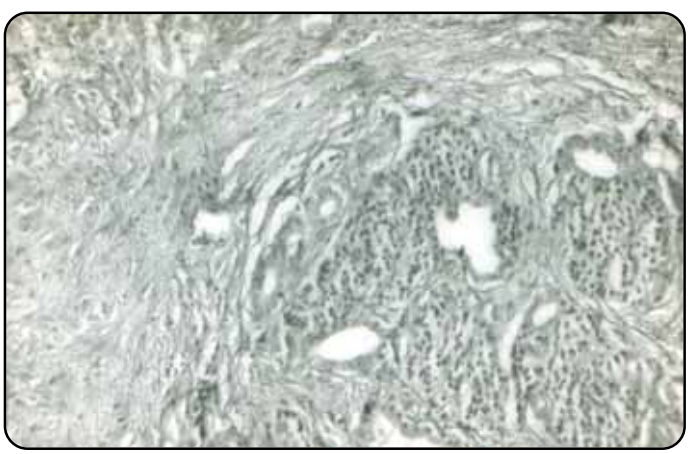


Fig. 12. Section from pancreas of a case of FCPD (H & E 100 x). Fibrous tissue. Nesidioblastosis seen around the ductules.



Chapter 22

Role of dietary factors in the etiology of fibrocalculous pancreatic disease and diabetes

Sandhyamani S

Summary

The pathogenesis of fibrocalculous pancreatic diabetes has been debated for years, and the role of dietary factors is at the forefront of proposed factors. In this article, the arguments for incriminating protein deficiency have been laid out in detail Particularly important is the occurrence of protein deficiency in combination with a high starch diet. This can lead to chronic pancreatic damage, particularly mucoid vasculopathy in large amount. Overall, data seem to suggest that it is the fact that starch is ingested in large amounts, and not particularly its quality, which is linked to pancreatic damage. This data, based mainly on animal studies, needs proof with human studies before it is accepted as a truism.

Introduction

In the middle of the last century, a pattern of peculiar diseases suddenly started appearing in near-epidemic proportions in certain developing regions of the world mainly in the peri-equatorial tropics [1,2]. Grouped as "tropical diseases" these included tropical chronic calculous pancreatopathy (TCCP) also called fibrocalculous pancreatic disease (FCPD) with diabetes, endomyocardial fibrosis, non-atherosclerotic forms of vascular disease called mucoid arteriosclerosis and idiopathic aortoarteriopathy, goitre and idiopathic epidemic neuropathy [3,4,5,6,7,8,9]. Initially reported from Uganda, Jamaica, Brazil and South Africa in the 1940's and 1950's, similar conditions were sporadically reported from other places including Brazil, Argentina, Nigeria and in large numbers from Kerala in India in the 1960's, 1970's and 1980's [1,10,11,12].

Clinico-pathological studies suggested toxico-nutritional factors, particularly dietary toxic factors in a background of low-protein high starch diets and deficiencies of vitamins and minerals, in the etiology of many of these diseases [64,7,13]. Various toxic factors suspected included cyanoglycosides from tapioca (cassava), a staple food in these regions, ergot-like toxins from plants and indigenous medicines, serotinin from bananas, trace heavy metals like thorium and cerium from the soil, and under-nutrition, associated with dietary deficiencies of protein and amino acids, especially tryptophan, cysteine and methionine,

minerals like iodine and magnesium [11,7,14,15,9]. However, there was no definite experimental proof available despite intense studies carried out on each of these diseases by several groups of research workers from different countries during the last five decades. It was however apparent that "cracking the etiogenic code" for any one of these conditions would help us understand the etiopathogenesis of all these diseases, since they seemed to have common clinico-epidemiological features and nutritional factors [16].

Autopsy studies at SCTIMST, Trivandrum, by this author, lead to the identification of a hitherto unrecognized acquired metabolic disorder presenting as an arteriosclerotic vascular disorder "mucoid vasculopathy", with generalized deposition of abnormal acid mucopolysaccharides (proteoglycans) in the walls of blood vessels and in connective tissues [17,18,19]. Mucoid vasculopathy was similar to mucoid arteriosclerosis described from Uganda and intimomedial mucoid degeneration reported from South Africa and was responsible for a variety of occlusive and aneurysmal vascular diseases in Kerala [18,20]. The vasculopathy was associated with the pattern of "tropical diseases" found elsewhere and was therefore considered to be part of a metabolic syndrome, sharing common etiological factors, possibly, toxico-nutritional factors [17,2].

The autopsies also showed early FCPD-like pancreatic lesions associated with mucoid vasculopathy of the pancreatic blood vessels [under publication]. Similar pancreatic and vascular lesions were produced in bonnet monkeys by dietary means, with low-protein high-starch tapioca and cornstarch-based diets resembling that eaten by people from Kerala where mucoid vasculopathy was observed [2,21,22,23]. The experiments established a non-human primate model for nutritional pancreatopathies, mucoid vasculopathy and associated metabolic disorder [2,24,25]. The bonnet monkey model showed that protein carbohydrate malnutrition due to nutritional imbalances with such diets, not toxic dietary factors from tapioca, was responsible for these conditions [26]. The lesions were produced by both sources of carbohydrate, hence high levels of starch of any source, such as rice and tubers, in conjunction with mild to moderate protein-deficiency

may cause these specific cardiovascular and pancreatic lesions [2,24]. This article traces various hypotheses advanced during the last 50 years for understanding the role of toxico-nutritional factors in the etiopathogenesis of FCPD, a unique form of pancreatic disease that is fast disappearing from the Indian subcontinent.

Pathology of FCPD

Detailed descriptions of the pathology of FCPD were based on observations in a few autopsy studies [4,27] and from excised surgical specimens [28,29]. These cases represented a late and end-stage of the disease process when the pancreas had become "cirrhotic" and structurally damaged beyond repair. Incidental pancreatic lesions reflecting early FCPD-like changes in Kerala population were noticed in routine autopsies (both cardiovascular and neurological cases) carried out at SCTIMST, Trivandrum [under publication]. Such observations helped in understanding the nature of early lesions, including vascular lesions that lead to FCPD and its etiopathogenesis.

In human autopsies examined at SCTIMST, the pancreas was generally small- sized, firm, with small shrunken lobules separated by streaks of fibrous tissue and showing intraductal sand-like calculi also in an occasional case. The atrophy was more marked in the distal parts of the gland. The most important and constant feature observed was mucoid vasculopathy of pancreatic artery and vein in all these cases. The artery was firm and thick with narrow lumen and having large amounts of abnormal acid mucopolysaccharides in its wall [17]. Such changes were most obvious in the main artery and its larger branches. Pancreatic lobules showed moderate atrophy of acini, large hypertrophied islets and some nesidioblastosis. There was mucoid metaplasia of duct epithelium. Ducts and intralobular ductules were lined by tall columnar epithelium and contained mucin plugs admixed with eosinophilic secretions. Hypertrophied nerve bundles and autonomic ganglia were occasionally seen, similar to those described in other autopsies with mucoid vasculopathy [30]. There was a distinct periductal and periductular fibrosis with patchy atrophy of the lobules, replaced by adipose tissue, however there was no inflammation of the parenchyma. Consequently, in a Workshop on Diabetes in the Tropics, it was decided

that the term "pancreatopathy" should replace "pancreatitis" to emphasize the non-inflammatory nature of FCPD lesions [31].

In reports on surgically excised and autopsy specimens, the exocrine pancreas was described as a shrunken markedly atrophic gland, replaced by dense fibro-adipose tissue, with an extreme form called "lipomatous atrophy" in which remnant islands of islet tissue were all that remained of the gland [28,29,27]. Nesidioblastosis was a very important feature described by Balaraman Nair that suggested active attempts at regeneration even in an atrophic gland [28,29]. Numerous calculi and inspissated eosinophilic secretions were seen within dilated ducts. Chronic inflammation was mainly around ducts containing calculi and was absent within the atrophic lobules [4,28,29]. Hypertrophied arteries with thick walls and mucoid degeneration were found within the gland [29]. Such changes were initially considered to be sequelae of chronic inflammation, scarring and ischemia. However since the main pancreatic artery was not available in the excised surgical specimen and autopsies in the population otherwise showed a generalized arteriosclerosis, not restricted to the pancreas, the occurrence of mucoid vasculopathy in the pancreatic vasculature and its role in the pathogenesis of FCPD were not recognized till recently [Balaraman Nair, and (late) JNP Davies, personal communications].

Salient clinical and epidemiological data regarding etiology of FCPD

- Found mainly in tropical and subtropical developing regions of the world [32].

- Seen in moderately nourished young individual with brittle diabetes, not prone to ketosis, associated with abdominal pain (therefore called pancreatitis), pancreatic calculi, varying degree of deficiency of exocrine pancreas [33]. FCPD was classified as a secondary form of diabetes mellitus and placed under Type 3 Diabetes in the recent WHO classification, clubbed with protein deficiency diabetes mellitus (PDDM), under malnutrition related diabetes mellitus (MRDM) [34].

Table 1. Dietary factors: summary of the evidence

- Association with the pattern of "tropical diseases," in the region, and co-occurrence these diseases in the same individual [1,35].
- Patient did not have gross malnutrition or a history of severe malnutrition in childhood [36]. Obesity, macro-vascular disease and atherosclerosis were absent in most patients [10].
- Patient often had a characteristic facies, due to bilateral parotid swelling [37].
- Pancreatic adenocarcinoma was an important late sequel [38].
- FCPD was absent in places where kwashiorkor was common [39,4] and also in people with better nutrition subsisting on tapioca [40]; but found in certain rice eating populations from Orissa and Tamil Nadu in India [32,33].
- Patients of FCPD were not alcoholic [39]
- Characteristic diet consumed was a low-protein low-fat high-starch diet [39]. The patients mostly ate high starch monotonous foods comprised of tubers (particularly cassava or tapioca), rice and bananas that provided little protein [4,32].
- Histopathological features of FCPD did not resemble pancreatic changes in severe protein deficiency (kwashiorkor) in humans [41], nor in animal models for the same [42,43] and milder forms of isolated protein deficiency [44].
- Since tapioca was consumed as a staple, many considered a toxic etiology possibly due to cyanoglycosides from the tuber [45,46,47].
- Toxicity due to trace elements like thorium and cerium in association with magnesium deficiency, selenium deficiency, hyper-vitaminosis D with hypercalcemia, viral and genetic etiology, were some of the other aspects briefly studied in the patients from Kerala and elsewhere, but not proved to be causative for FCPD [10].

Reappraisal of experimental animal models for FCPD

A. Toxic etiology

To test if ingestion of toxic factors from cassava was the cause for FCPD, purified cyanoglycosides were injected into rats [45]. Raw tapioca tuber (bitter variety with high levels of cyanoglycosides) was fed to experimental animals like rats and dogs [48,49,50,51]. Combination with hyper-vitaminosis D was also studied in a few rabbit experiments [52]. Although transient hyperglycemia and a rise in serum levels of some of the pancreatic enzymes were observed in some of the animals, the pancreatic lesions consisted mainly of mild to moderate acinar atrophy but did not resemble the human disease exactly in any of the experiments. These results led to a failure of cyanoglycoside toxicity hypothesis for FCPD.

B. Dietary deficiency of protein

There were several experimental studies to test the effects of varying levels of protein deficiency on the pancreas in different species like rat, rabbit, dog, and rhesus and bonnet monkey [25,53]. With mild protein deficiency of 20% to 10% dietary protein, reduction of acinar enzyme content was directly proportional to degree of protein deficiency; below 10% it was inversely proportional [54], perhaps due to production of amylase by acinar cells in response to marginal increase in dietary starch.

Using diets with protein deficiency ranging from 2.5%, 5%, 7% and 10%, Wachstein et al [42] showed that the severity of acinar cell atrophy was related to the level of protein deficiency induced in experimental rats. In experiments with dietary protein below 2.5% [42,55], there was severe atrophy resembling changes described in kwashiorkor and starvation effects due to severe drought [41]. There was moderate acinar cell atrophy in rats and bonnet monkeys given diets with protein levels of 3.5 % to 4% [42,25]. Dietary protein content above 7% protected the pancreas in experiments by Wachstein et al [42]. Therefore moderate protein deficiency seemed to be necessary for significant histopathological changes to occur.

The islets, ducts and blood vessels were found to be relatively normal in all these protein deficiency experiments, as found in kwashiorkor by J.N.P. Davies [41]. In the rhesus monkey model for kwashiorkor and malnutrition-related diabetes mellitus, using 0% dietary protein, Bajaj et al reported "normal islet mass" with a hypo-functional gland producing inadequate insulin in their experimental animals [56]. The islet mass was calculated and expressed only by a mathematical extrapolation since they found the entire gland (acini and islets) to be severely atrophic [Dev MG, personal communication]. Hence protein deficiency per se as examined in all these experiments, did not produce lesions resembling human FCPD.

C. Low-protein high starch diets

Proximate analysis of tapioca tuber showed that it provided mainly starch and negligible amounts of protein [10]. Traditionally, in all cassava consuming regions, tapioca was served with fish or with pulses. Shaper had pointed out that FCPD patients usually ate a low-protein low-fat high-starch diet [39]. Hence it was considered that monotonous foods and dietary imbalances with low-protein high starch (not severe malnutrition with protein deficiency) might play a role in the development of FCPD as postulated for mucoid arteriosclerosis, endomyocardial fibrosis and goitre, also common in the same regions [2,25]. Experimental diets designed to resemble such diets, were used to develop an animal model for mucoid vasculopathy at SCTIMST, Trivandrum, with the support of DST, New Delhi. The bonnet monkey model also showed features of mucoid vasculopathy and early lesions of associated conditions, particularly cardiomyopathy resembling endomyocardial fibrosis, diffuse colloid goitre-like changes in the thyroid and pancreatopathy [2,24]. Sriramachari and Gopalan used similar low-protein high-starch diets to produce mucoid degenerative changes in the aorta of bonnet monkeys, however they did not study the pancreas in their animals [57].

A detailed study of the pancreas in the bonnet monkey experiments, carried out by the author with Prof. Balaraman Nair, demonstrated lesions ranging from pancreatic atrophy to early FCPD lesions, as described below [25].

Three groups of sub-adult bonnet monkeys were given the following diets, formulated and cooked each day: i) a protein deficient normal carbohydrate diet, ii) a protein deficient high carbohydrate diet, iii) a control diet with normal protein and carbohydrate, for 3 or 5 months experimental periods. Protein ranged from 20% in control diet to approximately 4% in the protein deficient diets that was given to all the test group animals. The experiments were conducted in two sets, using tapioca starch as the carbohydrate in the first set and cornstarch in the second set. Groundnut oil, vitamin and mineral mixture were dispensed equally in adequate quantities to all animals. After sacrifice, histopathological studies were carried out on the pancreas.

In all the test group animals given protein deficient diets, the pancreas showed atrophy, more in the tail end of the gland, particularly in animals fed low-protein high starch diets. There was lipomatous atrophy in some. Thick walled pancreatic arteries with diffuse narrowing of the lumen resembling human mucoid vasculopathy, were more prominent in protein deficient animals fed additional starch.

Microscopically, there were widespread changes and disarray affecting all parts of the pancreas in the test group animals. Lobular and acinar cell atrophy and loss of bipolar staining in acinar cells were more severe in animals fed low-protein diets. Whereas marked islet hypertrophy and hyperplasia (nesidioblastosis), mucoid metaplasia of ducts and arteries were found in protein deficient animals given additional starch diets, and for longer experimental periods. The ducts in these animals showed basal cell and goblet cell hyperplasia, epithelial stratification and papillomatosis with focal mild dysplasia in some. Proliferated and dilated ducts and ductules contained plugs of mucoid material admixed with eosinophilic secretions. There was fibrosis around ducts, ductules, blood vessels and within lobules. Enlarged autonomic ganglia and hypertrophied nerve bundles were seen in some. Inflammatory changes were not evident in any of the pancreas specimens. Both sources of carbohydrate, tapioca starch and cornstarch, produced identical lesions.

Table 2. Salient conclusions of the study

- Protein deficient animals developed pancreatic atrophy (resembling human PDDM lesions); in those fed protein deficient high starch diets, the pancreas showed changes akin to early changes of human FCPD. Mucoid metaplasia of ducts and blood vessels were seen in both categories, more prominently in animals given the low protein high starch diets.
- Both tapioca starch and cornstarch based diets produced the same changes, proving that toxic factors from tapioca were not responsible for initiating the pancreatic lesions.
- Identical lesions were produced with both sources of carbohydrate, tapioca starch and cornstarch; hence tapioca consumption is not the sole causative factor for FCPD. A high level of dietary starch of any source is important.
- Mucoid vasculopathy is an integral part of structural and functional pancreatic lesions of PDDM due to protein deficiency and FCPD due to nutritional imbalance with low-protein high carbohydrate diets. Hence it has a central role in the pathogenesis of these sub-types of malnutrition related pancreatopathies and diabetes mellitus.
- A non-human primate (bonnet monkey) model for FCPD and mucoid vasculopathy was established by dietary means. Nutritional imbalance with mild to moderate protein deficiency and high carbohydrate, particularly starch, is responsible for changes characteristic of FCPD [2,25].

Discussion

Dietary ingredients and nutritional imbalances

The development of pancreatic lesions in the bonnet monkey model explains how FCPD can occur in persons with milder forms of malnutrition and not severe malnutrition or kwashiorkor in childhood. People consuming tapioca but having only mild protein deficiency did not develop FCPD [40]. Dietary protein was possibly still at a protective level in that population. Moderate protein deficiency is necessary for development of FCPD.

FCPD was also reported in people consuming rice, not tapioca as a staple food [32,33]. Since identical lesions were produced in the bonnet monkey model by either source of carbohydrate, tapioca starch and cornstarch, tapioca alone is not a causative factor. Excess rice starch and moderate protein deficiency may also give similar results. This explains how FCPD may occur in rice-consuming regions in India. Likewise, consumption of high carbohydrate from other tubers and starchy foods would have the same effects.

Malnutrition and vascular disease

Long-term effects of childhood malnutrition and under-nutrition (even transient phases) need to be studied, since these affect the structure and function of the exocrine and endocrine pancreas, the total size and micro-architechture of the gland and most importantly its vasculature. Mucoid vasculopathic arteriosclerosis was the first lesion to occur in the bonnet monkey model, preceeding the development of cardiomyopathy and pancreatopathy [24]. It was generalized, affecting all blood vessels (macro and micro-vasculature of all organs). FCPD patients did not have hypercholesterolemia and atherosclerosis [10], but absence of macro-vascular disease as shown in several reports [33] does not mean they had normal blood vessels. An accurate diagnosis of the vascular lesions and metabolic markers will help in understanding the pathogenesis of various pancreatic lesions and types of diabetes mellitus.

The severity of mucoid arteriosclerosis limits optimum function of the pancreas. Repeated episodes of vasospasm may cause chronic ischemia and atrophy of the pancreas, especially at the tail end where most of the insulin-producing islets are located. Therefore with low-protein high starch diets the pancreas is subjected to a double insult – directly in the form of increased demands on the gland stimulating hypertrophy, hyperplasia and nesidioblastosis of the islets, and indirectly due to narrow blood vessels causing vascular compromise, relative ischemia and possible episodes of severe vasospasm in response to hyperglycemia. While mild vasoconstriction may stimulate release of insulin, severe vasoconstriction may also lead to focal necrosis of the pancreas that may be an important cause for episodes of acute abdominal pain. Antibodies described in some cases of FCPD [58] may have been

produced to pancreatic cellular antigens released from ischemic or necrotic tissue. Regenerative activity in FCPD seen as hypertrophy with marked variation in islet size and nesidioblastosis may be a reparative response to ischemia and necrosis following severe vasoconstriction. Hypertrophied nerve bundles and autonomic ganglia may influence vascular tone.

Pancreatic duct lesions, lithiasis and malignancy

Mucoid metaplasia of duct epithelium is an important feature of FCPD [29] and is also a direct effect of low-protein high-starch diets [25]. In the experimental bonnet monkeys, epithelial stratification, hyperplasia and papillomatosis in the larger ducts caused obstruction, the smaller inter- and intra-lobular ductules appeared dilated with pent-up eosinophilic and mucus secretions. Goblet cell metaplasia was seen throughout the duct system. Abnormal viscid mucus material produced by such cells may act as the nidus for stone formation, as described in human FCPD and certain forms of chronic pancreatitis [29]. Lithiasis is intraductal, there is no parenchymal calcification in FCPD. The term "tropical chronic calcific pancreatitis" was changed to "tropical chronic calculous pancreatopathy" or "fibrocalculous pancreatic disease" with diabetes, during a Workshop on Diabetes Mellitus in the Tropics [31].

FCPD patients had an increased risk of pancreatic malignancy, especially, adenocarcinoma, 10 to 15 years after onset of diabetes [38,59]. Prolonged metaplastic and dysplastic changes may predispose the duct epithelium to toxic factors and the development of malignancy.

Parotid and other exocrine glands

Bilateral parotid swelling described in FCPD patients [37] may be due to mucoid metaplasia affecting all exocrine glands, besides the pancreas. Similar changes were noticed in mucus glands of the trachea and bronchi in human autopsies with mucoid vasculopathy and in the bonnet monkey model (Sandhyamani, unpublished observations). In the animal model the parotid gland also showed mucoid metaplasia of duct epithelium [Sandhyamani, unpublished observations], however this aspect was not studied in detail.

Pathogenesis of nutritional pancreatopathies and diabetes mellitus

Structural integrity and the capacity of the pancreas to respond to metabolic demands will determine the onset of diabetes mellitus. The pancreas is small sized in lean persons with severe protein malnutrition in childhood and may be of normal size in those with obesity and continuous over-nutrition throughout [41,60]. In both categories, the gland has an apparent normal micro-architechture. In kwashiorkor and protein deficiency, islets showed initial hyperplasia and became normal sized after realimentation [41]. They did not have any abnormal cytological features. There were no permanent functional changes in most persons [10]. A few histopathological studies of the pancreas with maturity onset diabetes mellitus from the west showed degenerative changes with amyloid deposits and hyalinosis, possibly as ageing changes, causing impairment of the microvasculature of islets [61]. Such deposits were not described in PDDM and in FCPD from developing regions. Diabetes develops slowly in those with protein deficiency in childhood manifesting as PDDM in early adulthood and in those with over-nutrition and obesity, as maturity onset diabetes mellitus (MODM) by middle-age or later. The onset would depend on the degree of "relative-obesity" and dysmetabolic features in an individual and occurrence of precipitating factors like sudden changes in lifestyle and acute stress [18]. In both PDDM and MODM, there is a proportionate distribution of anatomical components. Structural disarray of the parenchyma, narrowness of the blood vessels and fibrosis are not as severe as in FCPD patients.

By contrast, in FCPD, pancreatic damage and metabolic changes occur at an accelerated pace because of the severity of abnormal and disproportionate cyto-architechture of the pancreas, fibrosis, disarray of the lobules and ducts, and marked arteriosclerosis. The FCPD patient may thus develop clinically manifest exocrine pancreatic disturbances, including lithiasis, and diabetes mellitus at a younger age, in childhood and adolescence itself, as reported in several studies [32,36]. Marked structural and functional disturbances of the pancreas are the hallmark of FCPD, as seen in cirrhosis of the liver. FCPD is rightly called cirrhosis of the pancreas.

In all three groups, namely, PDDM, FCPD and MODM, diabetes develops when a lean individual becomes "relatively obese" and there is a disparity between metabolic and functional demands of the body and the limited capacity of a structurally compromised pancreas. Fat-rich foods cause adiposity and atherosclerosis, as observed in developed regions in the west and in urban India. Obesity may be due to consumption of not only high-fat foods but carbohydrate-rich foods too, particularly high-starch foods that result in deposition of abnormal acid mucopolysaccharide material in the connective tissues and walls of blood vessels, typical of mucoid arteriosclerosis observed in Kerala [18]. Protein-carbohydrate malnutrition thus causes the pancreatic lesions, mucoid vasculopathy, the types of obesity, the patterns of dyslipidemia and diabetes mellitus more commonly seen in developing regions of the world. It is expected that long-term experiments and monitoring of insulin-glucose kinetics in the bonnet monkey model will establish the pathophysiology of nutritional pancreatopathies, particularly FCPD, and diabetes mellitus. The model may be used for understanding the development of late sequelae of FCPD, like lithiasis and cancer and for formulating preventive measures.

Fig. 1a,b,c. Pancreas from control bonnet monkey (fed normal-protein normal-carbohydrate diet) has sharp borders and grey-pink, fleshy lobules (a). Marked pancreatic atrophy is seen in animal fed a low-protein normal-carbohydrate diet (b). Lipomatous atrophy mainly in the distal half and mucoid vasculopathy of pancreatic (arrow) and superior mesenteric (arrow head) arteries are seen in pancreas (posterior view) of animal fed low-protein high-carbohydrate diet (c).

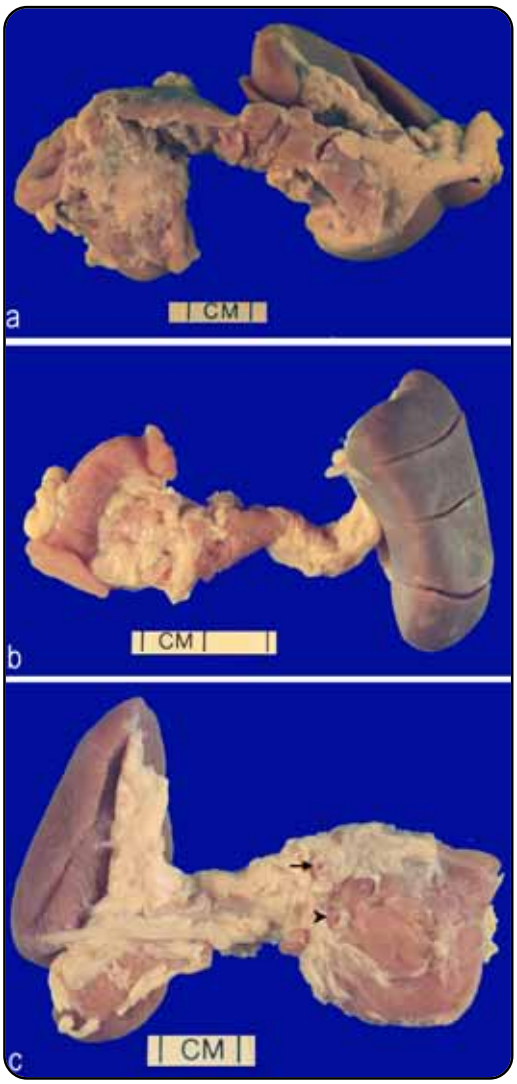
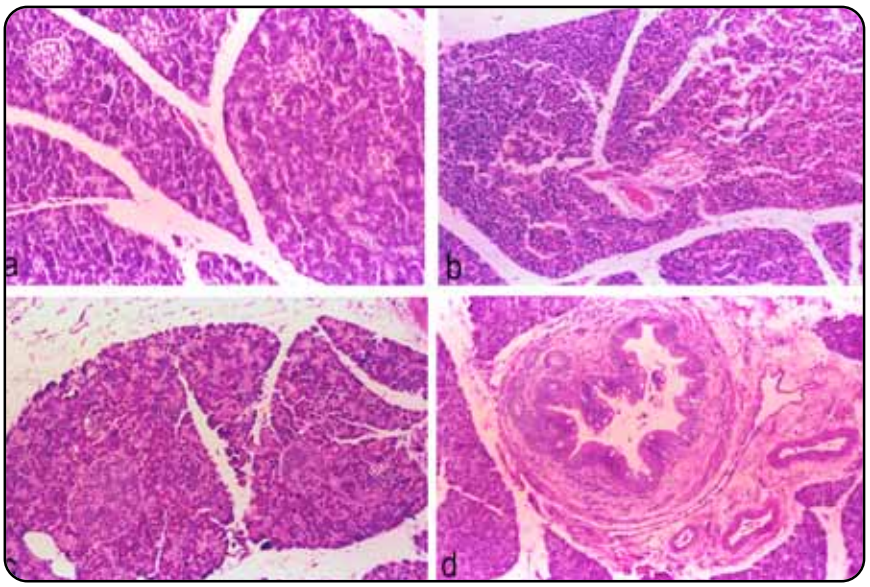


Fig. 2a,b,c,d. Pancreatic lobules from control animal (a), have sharp outlines, normal sized acinar cells with bipolar staining and small islets. Marked lobular and acinar cell atrophy and crowding of islets, is seen in protein-deficient animal (b). Pancreas from animal fed low-protein high-carbohydrate diet has moderately atrophic lobules with rounded outlines, hypertrophied islets and collections of pale eosinophilic secretions within dilated ductules. (c); the pancreatic duct (d) shows hyperplastic epithelium with mucoid metaplasia and inspissated mucoid secretions; thick-walled arteries are present in periductal fibrous tissue (d). [2a, b, c, d: H & E * 125].



References

1. Sandhyamani S. Mucoid vasculopathy and the nutritional imbalance metabolic syndrome In: Silverlines, ed, K. Radhakrishnan, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, 2004, 141-154.
2. Sandhyamani S, Valiathan MS, Saxena HMK. Cardiovascular changes in induced malnutrition. In: SERC Research Highlights. New Delhi: Department of Science and Technology, 1995:29-36.
3. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Geogr Med 1959;11:70-74.
4. Shaper AG. Aetiology of chronic pancreatic fibrosis with calcification seen in Uganda. Br Med J 1964;1:1607-1609.
5. Sonnet J, Brisbois P, Bastin JP. Chronic pancreatitis with calcifications in Congolese Bantus. Trop Geogr Med 1966;18:97-113.
6. Davies JNP. Endomyocardial fibrosis in Uganda. East Afr Med J 1948; 25:10.
7. Steiner IO, Hutt MSR. Vascular changes in the idiopathic peripheral gangrene of the tropics. Trop Geogr Med 1972;24:219-225.
8. Decker GAG, Samson ID, Schmaman A. Abdominal aneurysm in South African Negroes due to intimomedial mucoid degeneration. Br J Surg 1977;64:513-516.
9. Delange F. Endemic goitre and thyroid function in Central Africa. In: Falkner S, Kretchmer N, eds. Monographs in paediatrics. Vol 2. Basel: Karger, 1974:1-171.
10. Abu-Bakare A, Taylor R, Gill GV, Alberti KGMM. Tropical or malnutrition-related diabetes: a real syndrome? The Lancet 1986; May 17:1135-1138.
11. Geevarghese PJ, Pillai VK, Joseph MP, Pitchumoni CS. The diagnosis of pancreatogenous diabetes mellitus. J Assoc Physicians India 1962;10:173-180.
12. Balakrishnan V. Tropical pancreatitis. In: V. Balakrishnan ed. Epidemiology, pathogenesis and etiology in chronic pancreatitis in India. Trivandrum: Indian Society of Pancreatology. St. Joseph's Press, 1987:81-85.
13. Tylleskar T, Banea M, Bikangi N, Cooke RD, Poulter NH, Rosling H. Cassava cyanogens and konzo, an upper motorneuron disease found in Africa. Lancet 1992; 339:208-211.
14. Davies JNP. EMF – The beginning. In: Endomyocardial fibrosis. Ed. Valiathan MS, Somers K, Kartha CC. Oxford University Press, Delhi. 1993; Preface xiii – xiv.
15. Valiathan MS, Kartha CC, Nair RR, Shivakumar K, Eapen JT. Geochemical basis of endomyocardial fibrosis. In: Endomyocardial fibrosis. Ed. Valiathan MS, Somers K, Kartha CC. Oxford University Press, Delhi. 1993; 98-110.

16. Cooper K. Correspondence re: Sandhyamani S. Vascular lesions in an autopsy study (Mod Path 1993;6:333-341). Mod Pathol 1994;1:715.

17. Sandhyamani S. Mucoid vasculopathy: vascular lesions in an autopsy study. Mod Pathol 1993;6:333-341.

18. Sandhyamani S. Coronary artery disease in Asians: pathology and pathogenesis. In: H. R. Gundu Rao, V. V. Kakkar, eds. Coronary artery disease in South Asians; epidemiology, risk factors and prevention. South Asian Society on Atherosclerosis and Thrombosis (SASAT). New Delhi: Jaypee Brothers Medical Publishers (P) Ltd, 2001:61-91.

19. Sandhyamani S. Contribution on mucoid vasculopathy, in the chapter, Diseases of Blood Vessels. In: Illustrated Textbook of Cardiovascular Pathology by P Chopra, Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, 2003; pp 208-210.

20. Rajesh BJ, Sandhyamani S, Bhattacharya RN. A clinicopathological study of cerebral aneurysms. Neurology India 2004;52:82-86.

21. Sandhyamani S. Cardiovascular effects in bonnet monkeys (Macaca radiata) of cassava-based protein-deficient diet. Vet Hum Toxicol 1991;33:429-430.

22. Sandhyamani S. Vasculopathic and cardiomyopathic changes induced by low-protein high-carbohydrate tapioca based diet in bonnet monkey. Am J Cardiovasc Pathol 1992;4:41-50. Addendum: Am J Cardiovasc Pathol 1992; 4:277-279.

23. Sandhyamani S. Vasculopathic and cardiomyopathic changes induced by low-protein high-carbohydrate cornstarch based diet in bonnet monkey. Ann of the Nat Acad Med Sci 1997;33:61-67.

24. Sandhyamani S. A monkey model for mucoid vasculopathy. Int Angiol 1992;11:256-260.

25. Sandhyamani S, Vijayakumari A, Nair MB. Bonnet monkey model for pancreatic changes in induced malnutrition. Pancreas 1999;18:84-95.

26. Sandhyamani S. Low-protein corn-starch based diets exclude role of toxic factors from tapioca in induction of mucoid vasculopathy and associated disorders. In: G. T. Kurup, et. al. eds. Tropical Tuber Crops: Problems, prospects and future strategies. New Delhi, Calcutta: Oxford and IBH Publishing Co. Pvt. Ltd., 1996:467-476.

27. Nagalotimath SJ. Pancreatic pathology in pancreatic calcification with diabetes. In: S. Podolsky, M. Viswanathan, eds. Secondary diabetes: The spectrum of the diabetic syndromes. New York: Raven Press, 1980:117-145.

28. Balaraman Nair M, Latha P. Pancreas in chronic calcific pancreatitis. In: V. Balakrishnan, ed. Epidemiology, pathogenesis, and etiology in chronic pancreatitis in India. Indian Society of Pancreatology. Trivandrum: St. Joseph's Press, 1987:115-120.

29. Balaraman Nair M. Pathology of tropical calcific pancreatitis, Session I. In: N. Kumar, S. K. Acharya, eds. Proceedings of the first round table conference on tropical calcific pancreatitis. Trivandrum: Roussel Scientific, India, 1994:83-94.

30. Sandhyamani S. Mucoid vasculopathy of unknown etiology. Angiology 1991; 42:48-51.

31. Consensus Statement (Sandhyamani S, Participant). Consensus Statement on Diabetes Mellitus in the Tropics. International Workshop on Diabetes Mellitus Peculiar to the Tropics, Cuttack, October, 1995.

32. Tripathy BB, Samal KC. Overview and consensus statement on diabetes in tropical areas. Diabetes/Metab Rev 1997;13:63-76.

33. Mohan V, Mohan R, Susheela L, et al. Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile. Diabetologia 1985;28:229-232.

34. Alberti KGMM, Zimmet PZ. For the WHO consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part I. Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Med 1998;15:539-553.

35. Balaji LN, et al. Prevalence and clinical features of chronic pancreatitis in southern India. Int J Pancreatol 1994;15:29-34.

36. Mohan V, Snehalatha C, Bhattacharya PK, Ramachandran A, Viswanathan M. Nutritional profile of fibrocalculous pancreatic diabetes and primary forms of diabetes seen in southern India. Diabetes Res Clin Pract 1991;11:203-207.

37. Alapatt H, Ananthachari MD. A preliminary study of the structure and function of enlarged parotid glands in chronic relapsing pancreatitis by sialography and biopsy methods. Gut 1967; 8:42-45.

38. Narendranathan M. Chronic calcific pancreatitis of the tropics. Trop Gastroenterol 1981;2:40-45.

39. Shaper AG. Chronic pancreatic disease and protein malnutrition. Lancet 1960;1:1223-1224.

40. Tuescher T, Rosman JB, Baillod P, Tuescher A. Absence of diabetes in rural West African population with a high carbohydrate/ cassava diet. Lancet 1987; i:765-768.

41. Davies JNP. Essential pathology of kwashiorkor. Lancet 1948;1;317-320.

42. Wachstein M, Meisal E. Relation of dietary protein levels to pancreatic damage in the rat. Proc Soc Exp Biol Med 1954;85:314-317.

43. Deo MG, Ramalingaswami V. Production of peripheral fatty infiltration of liver in rhesus monkey by protein-deficient diet. Lab Invest 1960;9:319-329.

44. Svoboda D, Grady H, Higginson J. The effects of chronic protein deficiency in rats. II. Biochemical and ultrastructural changes. Lab Invest 1966;15:731-749.

45. McMillan DE, Geevarghese PJ. Dietary cyanide and tropical malnutrition diabetes. Diabetes Care 1979;20:202-208.

46. Geevarghese PJ. Calcific pancreatitis: causes and mechanisms in the tropics compared with those in the sub-tropics. Trivandrum: St. Joseph's Press,1986.

47. Pitchumoni CS. Special problems in tropical pancreatitis. Clin Gastroenterol 1984;31:941-959.

48. Mathangi DC, Deepa R, Mohan V, Govindarajan M, Namasivayam A. Long-term ingestion of cassava (tapioca) does not produce diabetes or pancreatitis in the rat model. Int J Pancreatol 2000;27:203-208.

49. Pushpa M. Chronic cassava toxicity: an experimental study. MD (Pathology) Thesis, University of Kerala, 1980.

50. Geldof AA, Becking J, De Vries CD, Vander Veen EA. Histopathological changes in rat pancreas after fasting and cassava feeding. In Vivo 1992;6:545-551.

51. Kamulu BP. The effect of a nutritionally balanced cassava (manihot esculenta crantz) diet on endocrine function using the dog as a model. 1. Br J Nutr 1991;65:365-372.

52. Shenoy KT, Leena KB, Nair RB. Pancreatic changes (enzymes and histological) in an experimental model fed with cassava based diet. In: G. T. Kurup, et. al. eds. Tropical Tuber Crops: Problems, prospects and future strategies. New Delhi, Calcutta:Oxford and IBH Publishing Co. Pvt. Ltd., 1994:458-466.

53. Sandhyamani S. Animal model for fibrocalculous pancreatic diabetes. In: Fibrocalculous pancreatic diabetes. Ed. V. Mohan (under publication).

54. Pitchumoni CS, Scheele GA. Interdependence of nutritional and exocrine pancreatic function. In: V. L. W. Go, et. al. eds. The pancreas, biology, pathobiology and disease. New York: Raven Press, 1993:449-473.

55. Khardori R, Bajaj JS, Deo MG, Bansal DD. Insulin secretion and carbohydrate metabolism in experimental protein malnutrition. J Endocrinol Invest 1980;3:273-278.

56. Bajaj JS, Subba Rao G, Subba Rao J, Khardori R. A mathematical model for insulin kinetics and its application to protein-deficient (malnutrition-related) diabetes mellitus (PDDM). J Theor Biol 1987;126:491-503.

57. Sriramachari S, Gopalan C. Aortic changes in induced malnutrition. Ind J Med Sci 1957;11:405-409.

58. Hazra DK, Singh R, Singh B, Gupta MK, Aggarwal P, Mittal S. Autoantibodies in a tropical ketosis resistant but insulin dependant diabetes mellitus. In: Bajaj JS, ed. Diabetes mellitus in developing countries. New Delhi: Interprint, 1984: 165-167.

59. Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. Pancreas 1994;9:62-66.

60. Cruikshank AH. Non-infective pancreatitis. In: Pathology of the pancreas. Springer-Verlag. Berlin, Heidelgerg, New York, Tokyo; 1986; pp241-245.

61. Cruikshank AH. The pancreas in diabetes mellitus and haemachromatosis. In: Pathology of the pancreas. Springer-Verlag. Berlin, Heidelgerg, New York, Tokyo; 1986; pp 79-95.

Chapter 23

Endotherapy of chronic pancreatitis – the Indian experience

Reddy DN, Ong WC, Tandon M, Rao GV

Summary

Endotherapy remains an important therapeutic modality in the management of chronic calcific (tropical) pancreatitis. It offers a viable alternative to surgery and can be repeated with minimal morbidity. However, Endotherapy is not always an alternative to surgery although it is hoped that by early endoscopic and medical intervention, the subsequent need for surgery is at best delayed of not obviated.

Introduction

Chronic pancreatitis is a relentless disease with no curative treatment. The goals of therapy are palliative and possibly to delay progression of the disease[1]. The aims of palliative therapy are to alleviate pain, prevent attacks of pancreatitis, reduce pancreatic exocrine insufficiency and to possibly improve endocrine insufficiency. The role of lifestyle modification (alcohol and smoking cessation) must be emphasized to the patient.

The diagnosis of advanced chronic pancreatitis is clear with a typical history of recurrent persistent epigastric pain and radiological evidence of pancreatic calcification. In the absence of radio-opaque calcified calculi, endoscopic retrograde cholangiopancreatography (ERCP) is the next logical step. ERCP allows for detailed study of the main pancreatic duct and side branches thus assisting in both the diagnosis and planning of endoscopic or surgical therapy. With developments in magnetic resonance cholangiopancreatography (MRCP), the role of ERCP in solely imaging the pancreas will be relegated.

Pain, stones and strictures

In chronic calcific (tropical) pancreatitis, pain presents early and is the major clinical symptom. The etiology of pain remains debated: intraductal hypertension[2], increased pancreatic tissue pressure[3] , pancreatic ischemia[4], neural inflammation[5] and ongoing recurrent pancreatic injury have been described. Relief of intraductal hypertension and ductal drainage is the rationale for endotherapy in chronic pancreatitis. Associated increased pancreatic tissue pressure and repeated ischemia may interact further worsening the disease. Ductal

decompression may thus potentially delay progression of this disease. Additional causes of pain (pseudocyst and peptic ulcer disease) have to be excluded. Pancreatic cancer may complicate later stages of the disease[6].

Patient selection for endotherapy is essential. Only a subgroup of patients with pain will benefit from endotherapy. A mandatory pre-requisite is demonstration of a dilated pancreatic duct due to obstruction by a stricture or a stone, or both[7]. Drainage procedures are indicated only for patients with pain and marked morphological changes of chronic pancreatitis. An endoscopic classification for tropical pancreatitis has been proposed to aid in therapeutic decisions:

Table 1: Endoscopic classification of Tropical pancreatitis

Type I	MPD normal, only side branches involved
Type II	MPD dilated, no ductal strictures nor stones
Type III	MPD dilated, dominant stone or stricture in the head
Type IV	MPD dilated, stones thoughout the duct without strictures
Type V	MPD grossly dilated, stones and strictures thoughout the duct

Based on this classification, only patients with Type II – IV will benefit from endotherapy. Endotherapy will not benefit patients with only side branch involvement (Type I); patients with Type V will require surgical management.

Endotherapy for pain, stones and strictures revolves around the combined use of endoscopic pancreatic sphincterotomy (EPS), extracorporeal shock wave lithotripsy (ESWL), endoscopic stone extraction, and endoscopic stenting.

a) Endoscopic pancreatic sphincterotomy (EPS)

Endosopic pancreatic sphincterotomy is used mainly to facilitate stone extraction. However, when only ductal dilatation is demonstrated (Type II), ductal decompression is achieved via EPS with or without stent placement. Endoscopic sphincterotomy of the pancreatic duct in patients

with chronic pancreatitis is a fairly safe procedure with a high technical success rate [8] .

The technique of EPS remains variable. At the Asian Institute of Gastroenterology (AIG), EPS is performed over a guide wire placed into the pancreatic duct. Pure cutting current is preferred to avoid further papillary fibrosis. The direction of the cut is is between 12 to 2 o'clock (as opposed to the 11 o'clock direction of the biliary cut).

Other techniques have been described. Deviere[9] describes a 2 step process: first biliary sphincterotomy and then pancreatic septotomy (dual sphincterotomy). Endoscopic biliary sphincterotomy (EBS) as the first approach has the advantage avoiding the rare biliary complication occurring after primary EPS: some patients present with jaundice the day after EPS probably due to edema occurring at the level of the biliary sphincter. After biliary sphincterotomy, the pancreatic orifice is usually seen at 5 o'clock on the margins of sphincterotomy. Its orifice can often be better visualized by sucking a little bit of air into the duodenum, inducing its transient opening. When deep cannulation of the MPD has been achieved, pancreatic sphincterotomy or "septotomy" is performed using pure cutting current. The cut is done with the distal part of the cutting wire, at 12 o'clock, over a length of 5 to 8 mm (depending on the diameter of the MPD) to create the largest access. The technique of a needle knife over an initially placed pancreatic stent is technically demanding in the setting of chronic calcific pancreatitis.

b) Extracorporeal shock wave lithotripsy (ESWL)

In the presence of pancreatic ductal stones (Type III and IV), ESWL is required in addition to decompression procedures. Without ESWL, deep cannulation of the main pancreatic duct fails in 50% of patients with severe chronic calcific pancreatitis [9] . Impacted pancreatic calculi are especially difficult to manage. While impaction at the ampulla can be promptly relieved by needle knife dis-impaction, those impacted within the duct are better managed by subjecting them to ESWL initially. Combined with minimally invasive endoscopic decompression, ESWL has replaced open surgery as the initial modality of therapy. Fragmentation rates with ESWL range from 75% to 100% and lead to

complete stone clearance in 40% to 75% of patients [10-15]. Factors favouring for treatment success include (i) single stones (ii) the absence of strictures and (iii) a small stone burden. Although complete pancreatic stone clearance is ideal, it is successful endoscopic decompression with reduction in main ductal diameters that is statistically correlated with pain relief [16, 17] . Following treatment, complete pain relief and a decrease in pain intensity is reported in 32-75% and 65-100% of patients respectively. ESWL fragmentation of pancreatic ductal calculi in conjunction with endoscopic clearance of the main pancreatic duct is associated with significant improvement in clinical outcomes in most patients with chronic pancreatitis .

In AIG, ESWL is performed with an electromagnetic lithotripter (Dornier Delta compact) equipped with a bidimensional flouroscopic and in-line ultrasound "targeting facilities". Targeting of pancreatic duct calculi is performed via flouroscopic guidance for radio-opaque stones. When radiolucent stones are found, targeting is performed via the ultrasound scanner of the lithotripter or fluoroscopically using a nasopancreatic tube. Shockwave energy settings are adapted to the individual patient's tolerance and comfort. The aim of therapy was successful fragmentation of ductal stones (to less than 3 mm) to allow spontaneous or endoscopic ductal clearance.

The use of epidural anesthesia has provided better patient tolerance of the procedure despite a higher intensity setting. In addition, epidural anesthesia reduces patient physical movement especially that of the lower limbs that facilitates targeting and fragmentation of the stones. Optimal efficacy and rapid fragmentation of stones is thus achieved.

Although multiple stones can be tackled by repeated sessions of ESWL in combination with endoscopic extraction, due to the high cost of therapy and uncertain outcome, we prefer to manage these patients surgically. In chronic calcific (tropical) pancreatitis, the stone volume is generally larger and the calculi are harder than alcohol related chronic pancreatitis.

ESWL may occasionally be deferred for patients with radiolucent stones. These "protein plugs" are usually friable and can be spontaneously

passed if their size is small following endoscopic sphincterotomy alone.

c) Endoscopic extraction of pancreatic calculi and pancreatic duct stenting

All patients undergo ERCP following ESWL. Complete ductal clearance is occasionally observed following ESWL alone. When residual stone fragments are present, EPS is performed and fragments are extracted using balloon catheters or dormia basket. Stone extraction is related to its size and the presence of downstream strictures. Pancreatic stent placement is required if dominant strictures are present or when main pancreatic duct clearance is deemed inadequate. In the presence of pancreatic duct strictures, endoscopic dilatation of the stricture combined with stent placement would benefit this subgroup of patients, at least in the short-term [17]. Patients who have difficulty with access to medical care or follow up have pancreatic stenting performed prophylactically. These stents are removed at 3-6 months post procedure.

d) Long term results of endotherapy

Pancreatic endotherapy is effective as short-term intervention, but the long-term result remains disappointing. The failure to ductal decompression to relieve pain in short term is consistent with the multi-factorial etiology of pain in chronic pancreatitis. Surgical decompression provides immediate pain relief in 70-90% of patients. However, this diminishes with time so that only 50% of patients remain pain free at 5 years [20-22]. In a long-term multicentre follow up study, ductal decompression offered relief of pain in two-thirds of patients when used as the only form of treatment. One-quarter of patients had to undergo surgery [7] . No long term-randomized trials are available comparing endotherapy against surgery.

Only a minority of patients remains symptom free after prolonged stenting. Therefore, careful follow-up is required. These stents require exchange for a period of 1 year either at 2-4 month intervals or "on demand" when pain recurs. A reduction or relief of symptoms may predict potential benefit from surgery.

Pseudocyst, pancreatic ascites and pancreatic pleural effusions

Endotherapy can be considered as first line treatment for pseudocyst adjacent to the upper gastrointestinal tract as it is safe, effective and provides promising long term results [23] . Timing of endotherapy is best delayed approximately 4 weeks to allow the pseudocyst to mature. Earlier intervention may be necessitated by complications such as infection, hemorrhage, enteric or biliary obstruction, hydrothorax or uncontrolled pancreatic ascites.

Transmural drainage through the stomach (cystogastrostomy) is preferred for pseudocyst in the body and tail of the pancreas while those in the head are drained into the duodenum (cystoduodenostomy). An important concern in transmural drainage is potential bleeding from blood vessels interposed between the pseudocyst and gastroduodenal wall. Endoscopic ultrasound (EUS) or EUS-guided puncture of the pseudocyst eliminates this risk[24]. When the cyst contains clear fluid, a 10Fr double pigtail stent will adequately drain the cyst. In the presence of necrotic debris, placement of a naso-cystic catheter for irrigation in addition to a 10Fr stent is required. When thick necrotic material is present, initial dilatation of the tract using a controlled radial expansion (CRE) balloon followed by removal of necrotic material with a dormia basket prevents subsequent clogging of the stent. EUS-guided cystenterostomy of nonbulging pancreatic fluid collections [25] requires a cautious and skilled approach.

Transpapillary cyst drainage is preferred when cyst-duct communication is evident; complication rates are lower with transpapillary access (16%) than after the transmural approach (39%) [26] . Stents may be placed into the pseudocyst [27, 28]; when technically not feasible, the stents should be advanced to the site of ductal communication as close as possible to the pseudocyst. In the presence of associated ductal disruptions, stents may either bridge the disruptions or be placed into the pseudocyst [29].

Pancreatic ascites and pancreatic pleural effusions can be treated via placement of a transpapillary stent. In the presence of duct disruption or end fistula, the stent should be placed across the leak [29, 30] .

Biliary strictures complicating chronic pancreatitis

Bile duct strictures complicating chronic pancreatitis may treated via endoscopic biliary stenting. Unfortunately, long-term results are poor and surgical bypass is preferred. When surgery is contraindicated, long-term placement of stents may be considered.

Pancreas divisum

It is estimated that 5-7% of the population has pancreas divisum. When found in association with chronic calcific (tropical) pancreatitis, a relative obstruction to pancreatic drainage through the minor papilla may contribute to the disease. In this setting, minor papilla sphincterotomy is potentially beneficial. Access for minor papilla sphincterotomy is more difficult and requires a "long position" of the duodenoscope. The use of special catheters (metal tip or tapered cannula) in addition to the use of hydrophilic (Terumo) guide wires is required.

Risk management

The need for patient selection and risk management requires reiteration. Contraindications to endotherapy include patients with duodenal stenosis and patients with multiple stones and strictures (Type V). When malignancy is suspected, further evaluation or surgery is warranted.

Pancreatic duct manipulations carry a more than 20% risk of inducing pancreatitis. Endoscopic pancreatic sphincterotomy carries a high risk of hemorrhage and perforation than its biliary counterpart [31]. It is thus cautioned that such interventions be performed only in large volume centers where expertise is available. Pancreatic duct stenting is associated with complications of stent migration, sepsis, perforation and ductal changes.

Minor reported complications of pancreatic ESWL are exacerbation of pancreatitis, mild abdominal discomfort and asymptomatic hyperamylasemia. Serious complications reported include hepatic subcapsular hematoma [32], splenic rupture with life-threatening hemorrhage [33], splenic abcess formation [34] gastric submucosal hematoma, cholangitis, pancreatic related sepsis and fluid collections [35]. Complication rates reported range from 0-20% of cases.

References

1. Reddy DN, Sriram PV, Das G, Rao GV. Endoscopic treatment of pancreatic disorders. Trop Gastroenterol 2001; 22(3):149-154.
2. Bradley EL, III. Pancreatic duct pressure in chronic pancreatitis. Am J Surg 1982; 144(3):313-316.
3. Ebbehoj N, Borly L, Bulow J, Rasmussen SG, Madsen P. Evaluation of pancreatic tissue fluid pressure and pain in chronic pancreatitis. A longitudinal study. Scand J Gastroenterol 1990; 25(5):462-466.
4. Reber HA, Karanjia ND, Alvarez C et al. Pancreatic blood flow in cats with chronic pancreatitis. Gastroenterology 1992; 103(2):652-659.
5. Bockman DE, Buchler M, Malfertheiner P, Beger HG. Analysis of nerves in chronic pancreatitis. Gastroenterology 1988; 94(6):1459-1469.
6. Misra SP, Thorat VK, Vij JC, Anand BS. Development of carcinoma in chronic calcific pancreatitis. Int J Pancreatol 1990; 6(4):307-312.
7. Rosch T, Daniel S, Scholz M et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy 2002; 34(10):765-771.
8. Jakobs R, Benz C, Leonhardt A, Schilling D, Pereira-Lima JC, Riemann JF. Pancreatic endoscopic sphincterotomy in patients with chronic pancreatitis: a single-center experience in 171 consecutive patients. Endoscopy 2002; 34(7):551-554.
9. Deviere J. Endoscopic therapy of chronic pancreatitis. Acta Gastroenterol Belg 2003; 66(2):184-188.
10. Delhaye M, Vandermeeren A, Baize M, Cremer M. Extracorporeal shock-wave lithotripsy of pancreatic calculi. Gastroenterology 1992; 102(2):610-620.
11. Sauerbruch T, Holl J, Sackmann M, Paumgartner G. Extracorporeal lithotripsy of pancreatic stones in patients with chronic pancreatitis and pain: a prospective follow up study. Gut 1992; 33(7):969-972.
12. Dumonceau JM, Deviere J, Le Moine O et al. Endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones: long-term results. Gastrointest Endosc 1996; 43(6):547-555.
13. Costamagna G, Gabbrielli A, Mutignani M et al. Extracorporeal shock wave lithotripsy of pancreatic stones in chronic pancreatitis: immediate and medium-term results. Gastrointest Endosc 1997; 46(3):231-236.
14. Neuhaus H. Fragmentation of pancreatic stones by extracorporeal shock wave lithotripsy. Endoscopy 1991; 23(3):161-165.

15. Van der HR, Plaisier P, Jeekel J, Terpstra O, den Toom R, Bruining H. Extracorporeal shock-wave lithotripsy of pancreatic duct stones: immediate and long-term results. Endoscopy 1994; 26(7):573-578.

16. Delhaye M, Vandermeeren A, Baize M, Cremer M. Extracorporeal shock-wave lithotripsy of pancreatic calculi. Gastroenterology 1992; 102(2):610-620.

17. Brand B, Kahl M, Sidhu S et al. Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic calcific pancreatitis. Am J Gastroenterol 2000; 95(12):3428-3438.

18. Kozarek RA, Brandabur JJ, Ball TJ et al. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc 2002; 56(4):496-500.

19. Rosch T, Daniel S, Scholz M et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. Endoscopy 2002; 34(10):765-771.

20. Sarles JC, Nacchiero M, Garani F, Salasc B. Surgical treatment of chronic pancreatitis. Report of 134 cases treated by resection or drainage. Am J Surg 1982; 144(3):317-321.

21. Sato T, Miyashita E, Yamauchi H, Matsuno S. The role of surgical treatment for chronic pancreatitis. Ann Surg 1986; 203(3):266-271.

22. Warshaw AL, Popp JW, Jr., Schapiro RH. Long-term patency, pancreatic function, and pain relief after lateral pancreaticojejunostomy for chronic pancreatitis. Gastroenterology 1980; 79(2):289-293.

23. Neuhaus H. Therapeutic pancreatic endoscopy. Endoscopy 2004; 36(1):8-16.

24. Sriram PV, Kaffes AJ, Rao GV, Reddy DN. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts complicated by portal hypertension or by intervening vessels. Endoscopy 2005; 37(3):231-235.

25. Sanchez CE, Maalak A, Le Moine O et al. Endoscopic cystenterostomy of nonbulging pancreatic fluid collections. Gastrointest Endosc 2002; 56(3):380-386.

26. De Palma GD, Galloro G, Puzziello A, Masone S, Persico G. Endoscopic drainage of pancreatic pseudocysts: a long-term follow-up study of 49 patients. Hepatogastroenterology 2002; 49(46):1113-1115.

27. Barthet M, Sahel J, Bodiou-Bertei C, Bernard JP. Endoscopic transpapillary drainage of pancreatic pseudocysts. Gastrointest Endosc 1995; 42(3):208-213.

28. Binmoeller KF, Seifert H, Walter A, Soehendra N. Transpapillary and transmural drainage of pancreatic pseudocysts. Gastrointest Endosc 1995; 42(3):219-224.

29. Kozarek RA, Ball TJ, Patterson DJ, Freeny PC, Ryan JA, Traverso LW. Endoscopic transpapillary therapy for disrupted pancreatic duct and peripancreatic fluid collections. Gastroenterology 1991; 100(5 Pt 1):1362-1370.

30. Deviere J, Bueso H, Baize M et al. Complete disruption of the main pancreatic duct: endoscopic management. Gastrointest Endosc 1995; 42(5):445-451.

31. Carr-Locke DL. Endoscopic therapy of chronic pancreatitis. Gastrointest Endosc 1999; 49(3 Pt 2):S77-S80.

32. Hirata N, Kushida Y, Ohguri T, Wakasugi S, Kojima T, Fujita R. Hepatic subcapsular hematoma after extracorporeal shock wave lithotripsy (ESWL) for pancreatic stones. J Gastroenterol 1999; 34(6):713-716.

33. Leifsson BG, Borgstrom A, Ahlgren G. Splenic rupture following ESWL for a pancreatic duct calculus. Dig Surg 2001; 18(3):229-230.

34. Plaisier PW, den Hoed PT. Splenic abscess after lithotripsy of pancreatic duct stones. Dig Surg 2001; 18(3):231-232.

35. Costamagna G, Gabbrielli A, Mutignani M et al. Extracorporeal shock wave lithotripsy of pancreatic stones in chronic pancreatitis: immediate and medium-term results. Gastrointest Endosc 1997; 46(3):231-236.

Chapter 24

Chronic calcific pancreatitis – Results of surgical management at SGPGIMS, Lucknow

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Summary

We present our surgical experience in subjects with chronic calcific pancreatitis. The most common indication for surgery was intractable pain. On comparing chronic calcific pancreatitis (CCP) subjects with those having alcoholic pancreatitis, we found that the prevalence of diabetes was similar. However, while subjects with CCP had a higher prevalence of calcification, those with alcoholic pancreatitis had a higher prevalence of local complications like pseudocyst, pseudoaneurysm and portal hypertension. We also describe our experience with drainage as well as resectional procedures. At our center, there has been a distinct shift in policy in the past decade - from that of surgical intervention limited to patients with rigid indications only, to a more liberal indication of surgical drainage especially where the anatomy is favorable.

Introduction

Chronic calcific pancreatitis (CCP) is considered a disease of the tropics, but several reports are there from the subcontinent spreading over the sub-tropical region. It is unclear whether the CCP seen in the sub-tropical region is similar to that of the tropics or to that of the Western hemisphere. We present our experience of surgical management of patients with CCP requiring surgical intervention.

Experience at SGPGIMS

Between January 1989 to July 2004, 161 patients with a diagnosis of CCP were seen in the Department of Surgical Gastroenterology at SGPGIMS, Lucknow. 141 of these underwent surgical intervention. The details of demography, clinical presentation, surgical procedures and outcome are presented.

Patients seen at SGPGIMS were residents of Uttar Pradesh (UP) with a sprinkling of patients hailing from the adjoining states of Madhya Pradesh and Bihar. There were no high-density pockets in the state and patients were uniformly distributed across the southeastern districts of UP. (Figure)

The median age of our patients was 33 (10-62) years. There were 98 men and 43 women. The etiology of CCP was idiopathic tropical pancreatitis in 115 (82%) and alcoholic in 26 (18%). Pain (n=136; 96%) was the commonest presenting complaint. The other presenting symptoms included jaundice (n=29; 20%), cholangitis (n=14; 10%), GI bleed (n=6; 4%), pancreatic ascites (n=2) and gastric outlet obstruction in one patient. Thirty nine (27%) patients had diabetes and 13 (9%) had clinical steatorrhea. Compared to idiopathic calcific pancreatitis (table 1), patients with chronic calcific alcoholic pancreatitis were men of older age and had a higher incidence of disruptive complications like pseudocyst and pseudoaneurysm. The pancreatic duct was of smaller diameter (5.7 mm Vs 8.4 mm) in chronic calcific alcoholic pancreatitis.

The median duration of pain at presentation was 36 (1-192) months. Objective categorization of pain was done in 108 patients based on the scoring system reported by Nundy et al. Patients were categorized into severe (53; 50%), moderately severe (45; 40%) and mild pain (10;10%).

Patients were evaluated with USG, CECT and ERCP depending upon the presentation and associated complications. In the last two years, a significant number of our patients are undergoing evaluation with MRCP (n=55; 40%). On evaluation, biliary obstruction was diagnosed in 29 (21%), pseudocyst was present in 26 (19%) and portal hypertension in 20 (14%) patients. Pancreatic cancer in association with CP was diagnosed in 9 (6.3%) patients.

The indication for surgery in these 141 patients and the surgical procedures performed are shown in Tables 2 and 3. 15 (10%) patients had postoperative complications; major among these being wound dehiscence (n=2), pancreatic fistula (n=4), GI bleed (n=4) and intra-abdominal bleed (n=2). Three patients required re-exploration and there was one postoperative death.

On follow up, all patients with jaundice, cholangitis and bleeding had relief of their symptoms. Of the 104 patients with pain as the indication for surgery, follow up is available in 88 patients. The median duration of follow up is 12.6 (mean 16.7m, range 1-75) months. Seventy six percent are pain- free whereas 16%, 1% and 5% have mild, moderate

and severe pain respectively on follow up. Two patients died while on follow up.

Fourteen patients underwent a prospective study to assess the effect of ductal decompression on pancreatic exocrine and endocrine function. Pancreatic endocrine function was evaluated by an oral glucose tolerance test and measurement of C-peptide levels while the exocrine function was evaluated by measuring the fecal chymotrypsin and serum trypsinogen levels. Patients underwent the evaluation preoperatively and on follow up at least after six months of surgery. In this study, there was no significant improvement in beta cell function or exocrine function on follow up of 6-12 months. There was a significant fall in the elevated serum trypsin levels following surgery suggesting resolution of sub-clinical inflammation.

Nine (5.3%) patients of associated malignancy of the pancreas were also seen during this period. All patients had significant pain of a median duration of 6.5 mo. Four (44%) patients had jaundice on presentation of a median duration of 5.5 weeks. A palpable epigastric mass was present in 4 patients. Five (55%) patients had steatorrhea and 6 (66%) had associated diabetes mellitus. On imaging, calcifications (all patients), mass in the head (n=4) and body (n=1) of the pancreas, and vascular infiltration (n=1) and liver metastasis (n=1) were present.Eight patients underwent surgical exploration with resection (pancreaticoduodenectomy) being performed in only one patient. Other patients underwent biliary bypass (n=5), lateral pancreaticojejunostomy ((n=5) and gastrojejunostomy (n=3). Tumor was located in the head region in all except the one with body tumor.

Conclusions

The philosophy of surgical treatment of patients with CCP at SGPGIMS has evolved over the past decade. There has been a distinct shift in policy in the past decade; from that of surgical intervention confined to patients with strict indications, to more liberal indications of surgical drainage, especially where the anatomy is favorable. This shift is based on the premise that perhaps early surgical decompression may halt the progressive deterioration of pancreatic function, although this premise

needs to be documented in larger number of patients with longer follow up.

Fig: State and district-wise distribution of patients seen at SGPGIMS, Lucknow

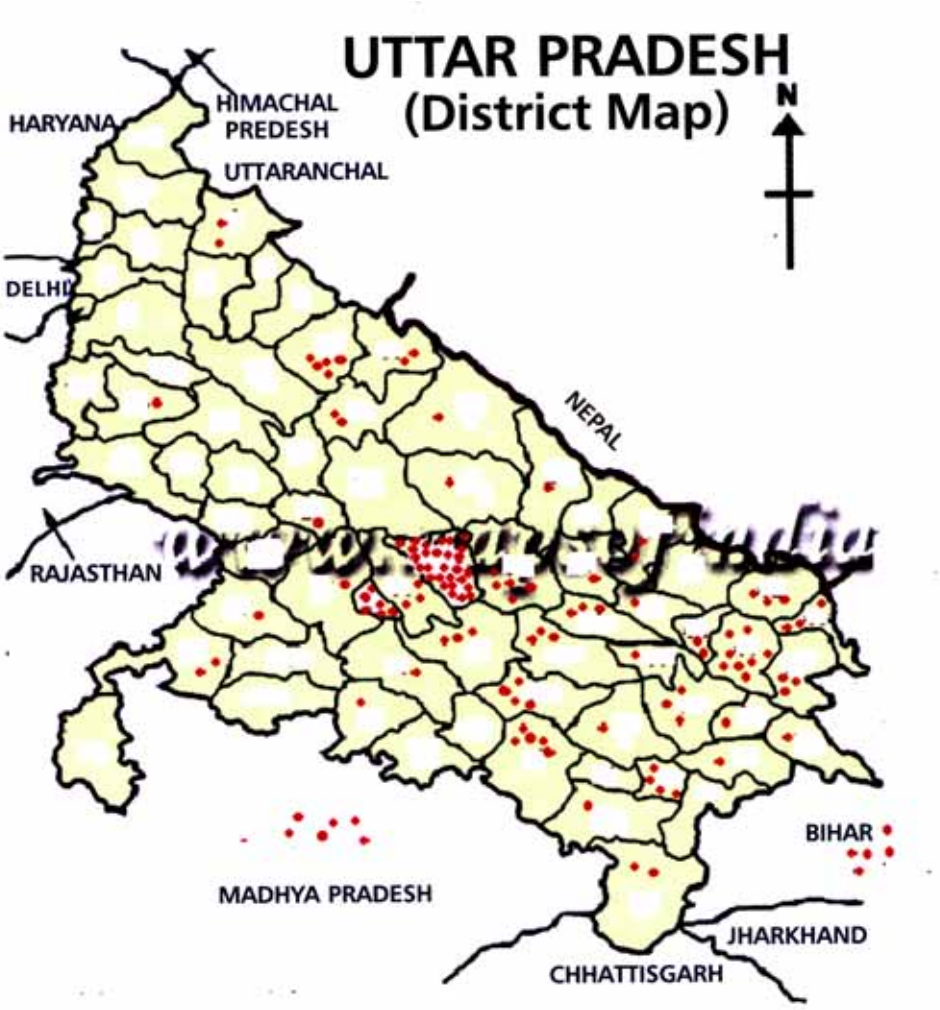


Table 1: Comparison of tropical and alcoholic chronic pancreatitis

	Tropical pancreatitis (n=115)	Alcoholic pancreatitis (n=26)
Median age (yrs)	30 (10-62)	45 (30-58)*
Male: female	74:41	26:0
Pain (%)	96	96
Jaundice (%)	18	28
GI bleed (%)	4	8
Steatorrhea (%)	9	8
Diabetes (%)	27	28
Median pain duration (months)	36	36
Portal hypertension (%)	13	20
Pseudocyst (%)	10	60*
Pseudoaneurysm (%)	-	16*
Mass on CT scan (%)	10	8
Calcification (%)	90	55
Associated malignancy (%)	6	4
Serum amylase (SI)	30	74*
Serum ALP (IU/L)	143	241*
Diameter of PD (mm)	8.4	5.7*
Resectional procedures (%)	13.5	24
Morbidity (%)	22	28

*$p < 0.05$

Table 2: Indications of surgery in 141 patients

Intractable pain	105 (73.5%)
Pain with	
Jaundice	13 (9%)
Bleeding	5 (3.5%)
Cholangitis	4 (3%)
Painless jaundice	7 (5%)
GI bleed	2 (1.5%)
Pancreatic mass on imaging	4 (3%)
Duodenal obstruction	1

Table 3: Surgical procedures performed in 141 patients

Pancreatic Procedures (N=128)	
Drainage procedures	
Duval's procedure	1
Lateral PJ	88
Frey's procedure	15
Resectional procedures	
Pancreaticoduodenectomy	6
Distal pancreatectomy	8
Cyst drainage procedures	
Internal	5
External	5
Associated procedures	
Biliary procedures	26
Gastro-jejunostomy	3
Excision of pseudoaneurysm	4
Splenectomy	17
Non-pancreatic procedures only (N=13)	
Biliary procedures	8
Triple bypass	3
Splenectomy	2

Chapter 25

Surgery in chronic pancreatitis - the Chandigarh experience

Wig J D, Yadav TD, Gupta R, Gupta V

Summary

We discuss our experience with surgery for chronic pancreatitis. At our center the morbidity of surgical therapy is about 7%. There has been no mortality thus far. Surgery is an effective mode of therapy, and in our experience, Frey's operation gave good results. The choice of the operative procedure should be adopted individually for each patient depending on the clinical profile, particularly important considerations being morphological preservation of pancreatic tissue, obtaining relief of pain and minimizing the risk of bleeding complications.

Introduction

Chronic pancreatitis (CP) is a complex disease characterized by a progressive inflammatory disease of the pancreas often associated with complications. The advantages of surgical intervention are: relieves pain which is the most distressing symptom, drains all components of a chain of lakes pancreatic duct (PD), removes pancreatic ductal stones which are densely adherent to the duct wall, deals with complications of CP and is the final modality to diagnosis or rule out malignancy.

Indications for operative treatment- our experience

The indications for surgery in our experience are: intractable pain not alleviated by medical therapy, calculi in the pancreatic ductal system, head mass, with suspicion of malignancy and complications such as non-resolving biliary or duodenal obstruction, pseudocysts, pancreatic fistula, and left sided portal hypertension

Problems in surgical management

No single operation addresses all the structural abnormalities and complications associated with CP. When pain is the only symptom, selecting an operation is challenging.

Important steps in technique adopted

The goal of surgical treatment is preservation of exocrine and endocrine pancreatic function, pain relief, better long-term outcome, and

improvement of patient's quality of life. To achieve adequate pain relief it is important not to leave undrained any part of the obstructed ducts containing stone material, mainly in the head of the pancreas. A number of studies have shown that pancreatic head is the pacemaker of the disease in most patient with CP.

Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy (LPJ) (Frey's procedure) has been our procedure of choice with good results in achieving pain relief. Important steps of the operation include:

i) Resection of diseased tissue in the head of the pancreas and opening the main duct in the neck, body, and tail of the pancreas. Slices of pancreatic tissue are removed while coring out the head and uncinate process. We assess the thickness of remaining pancreas by palpation after Kocherization of the duodenum.

ii) All the ducts in the head of the pancreas are decompressed- the duct of Santorini, the duct to the uncinate and the duct of Wirsung and the tributaries associated with all the three ducts in the head of the pancreas. Unsuccessful operation is due to failure to address disease in the duct of Santorini and the duct to the uncinate and tributary ducts.

iii) Pancreatic head is resected nonanatomically leaving a rim of pancreatic tissue adjacent to the portal and mesenteric veins. It does not necesitate transection of the gland above the portal vein and thereby minimizes the risk of bleeding complication.

iv) A minute portion of the pancreatic tissue along the medial wall of the duodenum and to the left of the intrapancreatic portion of the common bile duct is preserved. The location of the common bile duct is ascertained by palpation. We have not found it necessary to perform a choledochotomy and stenting for this maneuver.

v) It should be possible to pass a probe freely into the duodenum through the duct of Wirsung opened close to the ampulla.

vi) Leaving the posterior capsule of the pancreatic head intact permits drainage of the head of the pancreas in continuity with the Roux-en-Y

limb used to drain the body and tail of the pancreas. Thus only one anastomosis to a Roux-en-Y limb suffices.

vii) In a patient with small duct disease, a longitudinal V- shaped excision of the ventral part of the pancreas into the pancreatic duct (Izbicki's modification of Frey procedure) has been found effective and allowed an efficient pancreaticojejunostomy. This was performed in one patient in the present study. Main duct was decompressed and Roux-en-Y limb was sewn to the capsule of the pancreas.

viii) Local resection of the head of the gland removes diseased tissue associated with the ducts and their tributaries in the head of the pancreas.

ix) LPJ drainage addresses the problems of obstructing calculi and strictures in the main pancreatic duct only. The advantage of this procedure is that pancreatic tissue in the neck, body and tail of pancreas is preserved.

x) The cored out tissue is subjected to histopathological examination. This procedure provides sufficient material to rule out malignancy on histopathological examination.

xi) When the coring out process was complete, we were able to palpate a shell of pancreatic tissue between the index finger held behind the head of the pancreas and the thumb in the cored out head of the pancreas. We prefer to employ cautery to accomplish head coring.

xii) Side to side Roux-en-Y pancreaticojejunostomy is constructed.

xiii) End to side jejunojejunostomy is placed approximately 40 cm below the pancreaticojejunostomy.

Complications of chronic pancreatitis

In our series, we encountered common bile duct stricture, duodenal obstruction, vascular abnormalities (splenic vein thrombosis with portal hypertension, pseudoaneurysms), and pancreatic ascites. One of our patients after head coring and extended drainage turned out to have a pancreatic carcinoma on histopathological examination.

Our experience

Thirty patients were seen in a two year period -24 males and six females, mean age was 38 years (15- 66). Alcohol abuse was present in 58% and cause could not be determined in 30%. Intractable abdominal pain was present in 90% of patients. Two patients had jaundice and five had portal hypertension. Six patients were diabetic at the time of presentation, weight loss was present in 14 patients, steatorrhoea in nine, pseudocyst in seven, and duodenal dystrophy in one.

Investigations

Imaging studies: X-ray abdomen showed calcification in nine patients. Contrast enhanced tomography scan was done in all patient and showed calcification in 26 patients. In most of our patients, calcification was predominantly in head and uncinate process. Dilated pancreatic duct was present in 29 patients. Associated pseudocyst was found in seven, and portal vein obstruction in five. Endoscopic pancreaticography was performed in five patients (ERCP) and magnetic resonance cholangio pancreaticography (MRCP) in five patients. ERCP showed deformed papilla in one and narrowed papilla in another patient, mild narrowing at D1 and D2 segment was present in one patient, dilated MPD with short segment of ventral duct was present in one suggestive of pancreas divisum, deformed and strictured MPD with leak from side branch was found in one patient with evidence of stones in MPD and side branches also. Endopancreatic stenting has been done in one patient.

MRCP showed grossly dilated MPD with stones in three patients, atrophic pancreas in one and disease confined to only head area including uncinate process in two patients. Dilated PD with stricture with evidence of large pseudocyst was found in one patient.

Operative procedures performed

Frey's procedure was performed in 14 patients, Izbicky's in one, head excavation in one, lateral pancreaticojejunostomy (LPJ) in one and distal pancreatectomy with devascularization procedure was performed in one patient.

Additional procedures

Roux–en-Y hepaticojejunostomy was performed in four patients, splenectomy in two, choledochojejunostomy in one, cholecystojejunostomy in one, cystogastrostomy in one, cysto pancreaticojejunostomy in one, and gastrojejunostomy in one patient. In four patients with portal hypertension no additional procedure was performed, two of these were diagnosed on operation table and the procedure was deferred. Two patients had associated biliary stricture and Roux-en-Y hepaticoje-junostomy was done. One patient had chronic pancreatitis with biliary stricture and only choledochojejunostomy was done because she did not have pain.

Morbidity and mortality

Total morbidity was 7%. One patient had intraabdominal bleed associated with upper gastrointestinal bleed. He was managed conservatively with blood transfusion and injection Octreotide 100μg subcutaneously thrice a day. Average hospital stay was 8.3 days (range 5-13 days). There was no mortality in our series.

Conclusion

In our experience Frey's operation gave good results. However, the choice of the operative procedure should be chosen- individually for each patient depending on the morphological preservation of pancreatic tissue, the need for pain relief always aiming to minimized risk of bleeding complication.

Chapter 26

Surgical management of tropical calcific pancreatitis – observations from Orissa

Mihir K Mohapatra

Summary

Surgery for tropical chronic pancreatitis (TCP) is essentially aimed at alleviating pain and improving the quality of life. At the same time, it must be done with a view to preserve the exocrine and endocrine function as well as to prevent local pancreatitis-related complications. This article reviews the experience with surgery as a management tool for TCP from Orissa, in the eastern part of India, and also puts forth a few key issues that future research must address.

Introduction

Chronic pancreatitis (CP) is a continuing inflammatory disease characterized by irreversible morphological changes that cause pain with or without permanent loss of function. Tropical chronic pancreatitis (TCP) is of unknown aetiology and is confined to tropical regions. It is calcific in nature and presents with pain (tropical calcific pancreatitis) or diabetes (fibrocalculous pancreatic diabetes, FCPD). Since the cause and natural course of this disease are unclear; the optimization of therapy has remained difficult. For the time being, as for chronic pancreatitis in general, management is aimed at either alleviating pain or other organ complications.

Any treatment planned should aim to remedy the cause, arrest the progression of the disease and relieve the symptoms. Management policy should take care to diagnose it early, establish the cause and plan therapy; which in turn should cease its progression and relieve the symptoms.

Non-operative treatment options such as endoscopic intervention, ESWL or both should be considered side by side with surgery. Apart from pain; involvement of other adjacent organs like distal bile duct and duodenal stenosis, segmental portal hypertension, pseudocyst and internal pancreatic fistula, unresponsive malnutrition and inability to exclude cancer; constitute indications for surgery.

The goals of surgery should be: pain relief, control of pancreatitis-associated complications of adjacent organs and preservation of exocrine and endocrine pancreatic function, as well as the improvement of quality of life

Evaluation of any surgical procedure should entail preoperative assessment of; exocrine and endocrine pancreatic functions, proper estimation of pain and quality of life. Indications of surgery in TCP include : severe, intractable pain, pancreatitis-associated complications of adjacent organs, distal common bile duct stenosis, duodenal stenosis, segmental portal hypertension, pancreatic pseudocyst with ductal pathology, internal pancreatic fistula and pancreatic ascites, exclusion of malignancy despite extensive workup, progressive destruction of the organ despite conservative treatment and, occasionally, progressive ill health and problems arising from malnutrition.

Rationale for surgical procedures

Pathogenesis of pain in chronic pancreatitis is either due to ductal and parenchymatous hypertension or perineural inflammation. Ductal ectasia, single or multiple strictures of the ductal system and obstruction of the ducts by stones are seen in the majority of these patients. Also, in a majority of patients with TCP, the problem lies in the head. Either it is an inflammatory mass, with or without adjacent organ involvement (bile duct, duodenum or the portal venous system), or stones or strictures in the ductal system. Surgical procedures have been developed to address the pathological changes and offer benefit to these patients. They are usually drainage or resectional procedures.

Drainage procedures: Caudal pancreaticojejunostomy (DuVal), lateral pancreaticojejunostomy following resection of the tail and the spleen (Puestow and Gillesby), and longitudinal pancreaticojejunostomy without these resections (Partington and Rochelle).

Resectional procedures: Classical pancreaticoduodenectomy (PD, Whipple's procedure), pylorus preserving pancreaticoduodenectomy (PPPD, Longmire- Traverso procedure), and the doudenum preserving pancreatic head resection (DPPHR, Beger's procedure).

Extended drainage procedures: Longitudinal pancreaticojejunostomy with local pancreatic head resection (LPJ- LPHE, Frey's procedure), longitudinal V-shaped excision of the ventral pancreas with pancreaticojejunostomy (Izbicki, for small duct disease).

Longitudinal drainage procedures such as Peustow, Gillesby; and Partington Rochelle without distal pancreatectomy and splenectomy gave no pain relief in 20 to 40 percent. Resectional procedures like Whipple's procedure, pylorus-preserving pancreaticoduodenectomy (Longmire-Traverso procedure), and duodenum-preserving resection of the head of the pancreas (DPRHP, Beger's procedure) gave pain relief in 80-90% patients. Extended drainage procedure such as longitudinal pancreaticoduodenectomy with local pancreatic head excision (LPJ-LPHE, Frey's procedure) combines drainage of Partington & Rochelle with excision of inflammatory head mass (the 'pace-maker') maintains the physiological gastroduodenal passage and the continuity of the CBD.

The results of surgery in chronic pancreatitis should take the following parameters into consideration. They are: relief of pain, morbidity rate, mortality rate, endocrine insufficiency, exocrine insufficiency, increase in body weight and occupational rehabilitation. The morbidity and functional impairment is definitely less with extended drainage procedures when compared with resectional procedures.

TCP/FCPD in Orissa

Review of case records revealed that 160 patients attended our department between April 1997 and October 2004, with the final diagnosis of chronic pancreatitis. All of them had calcification of the pancreas on ultrasonography. History of upper abdominal pain with or without diabetes had initiated the investigation leading to the diagnosis. More than 90% (n= 153) of them with chronic pancreatitis are nonalcoholic. Only 6 of them had a history of alcoholism. All these patients with idiopathic disease were classified classified as TCP/FCPD with the intention of having a preliminary estimate of the type and extent of this problem in our state. Males are affected about 3-4 times more often than females (table 1).

Table 1: Gender distribution of the study subjects

Gender	No.	Percentage
Male	117	76.5
Female	36	23.5
Total	153	100

Half of these patients are in the third and fourth decade of life. The disease never presented before the age of 10 and rarely remained silent until the age of 60 years (table 2).

Table 2: Age distribution of the study subjects

Age group	No.	Percentage
1-10	1	1
11-20	27	18
21-30	43	28
31-40	36	23
41-50	26	17
51-60	15	10
61-70	2	1
71-80	3	2
Total	153	100

Socioeconomically, our patients belonged to poor or lower middle class. Pain was present in about 97% of our patients. Severity and frequency of pain is relatively less in comparison to alcoholic chronic pancreatitis. Severe pain, meaning that which requires injectable potent analgesics like ketorolac, diclofenac or pentazocine, used to be infrequent, but when it occurred, lasted for short episodes like hours to few days only. Clinical steatorrhoea is rare and history of oily stools following fatty diet was elicited in a few patints on repeated questioning. Lab test of faecal fat estimation was not routinely done. Diabetes was present in only 12 (8%) of these patients. It used to be less severe and manageable in all of them. Surgical obstructive jaundice occurs in patients where the head is involved more (8%). Pancreatic head cancer and chronic pancreatitis do overlap (6%). In a case of pancreatic head mass, it is often difficult to exclude malignancy. Some kind of a cytological or histological evidence is necessary to make any surgical intervention. Duodenal stenosis and segmental portal hypertension are rare complications. Pseudocyst and pancreatic ascites are seen in some patients (table 3).

Table 3: Common presenting symptoms

Symptom	No.	Percentage
Pain	148	96.7
DM	12	7.8
Steatorrhoea (clinical)	0	-
Jaundice	7	4.5
Nutrition	-	
Ascites	1	0.6
Pseudocyst	11	7.1
Associated problems	7	4.6
Malignancy	5	3.2

Type of surgery and their results in TCP: Thirtyeight of our patients had surgical intervention. Pancreaticoduodenectomy was done in one patient with a limited and localized head mass. Cystogastrostomy and cystoduodenostomy were done in 8 patients. Cholecystojejunostomy was offered to 4 patients with obstructive jaundice and ill health. Twentyfive patients had pancreaticojejunostomy; out of which 13 had longitudinal pancreaticojejunostomy (Partington & Rochelle) and 12 had extended drainage (table 4).

Table 4: Surgical procedures

Procedure	No.	Percentage
Long PJ (Partington, Rochelle)	12	23
Frey's	16	31
Whipple's	2	4
Cystogastro/Cysto. Du	11	21
Cholecysto-J	4	8
Others	7	13
Total	52	100

Pain had recurred in 2 patients with longitudinal pancreaticojejunostomy. None of the patients with extended drainage procedure; which we are practicing since 1998, has developed pain yet. Endocrine insufficiency present in those before surgery has not worsened in the follow up period. Weight gain is common in these patients following drainage procedure (table 5).

Table 5: Results of surgery

Result	P-R	Frey's	Whipple's
Pain relief	10/12	15/16	-
Morbidity	1/12	0/16	-
Mortality	0/12	1/16	1/2
Exo-insufy status	0/12	0/16	-
Endo-insufy status	0/12	0/16	-
Rehabilitation	Good	Good	

Future research pointers

In conclusion, future work on surgical management of cases with tropical calcific pancreatitis/fibrocalculous pancreatic diabetes should try to find out answers for:

1. Can we tailor operation according to mechanism\origin of pain?
2. If surgery delays functional impairment, should it be performed routinely?
3. Is failure to thrive despite replacement in patients with FCPD a valid indication for surgery?
4. What is the role of endoscopic intervention and ESWL, alone or in combination?

Chapter 27

Surgery in Chronic Pancreatitis: the Deva Matha/PVS/Lakeshore experience

Ramesh H

Summary

We discuss our experience with surgery for chronic pancreatitis, and also comment on a proposal for a new grading system for the disease. The most common indication for surgery at our center was the setting of an inflammatory mass with a high suspicion of malignancy. 11 patients died in the postoperative period (mortality 2.6%). Major and minor complications occurred in 17% of cases. Excellent pain relief after surgery was seen with 56% of the cases. Early relapse of pain was related to technical factors, while persistent malabsorption as well as underlying malignancy accounted for the late relapses.

Introduction

Chronic pancreatitis implies an irreversible change in the parenchyma and ductal elements of the pancreas. The commonest causes of chronic pancreatitis in Kerala are a) the idiopathic or tropical pancreatitis and b) chronic pancreatitis due to alcohol abuse. Regardless of etiology, chronic pancreatitis affects young men and women in the prime of their lives and takes a heavy toll on the quality of life and productivity of the individual. Therapy is directed at relieving the symptoms and forestalling complications. In a subset of patients with chronic obstructive pancreatitis, however, complete reversibility of the pathology is a possibility. Chronic obstructive pancreatitis occurs due to obstruction of the pancreatic duct by a stricture or stone. Upstream dilatation of the duct results; there is little or no fibrosis and no calculi formation; functional changes in the pancreas are also minimal. This disease is treatable by ductal decompression. The pathogenesis of pain and complications in chronic calcifying pancreatitis is more obscure. Ductal/parenchymal hypertension, nerve inflammation, and pressure of pseudocysts have been the most acceptable etiological factors.

Approach to treatment planning for patients with chronic pancreatitis:

This is based on the following key questions: Does the patient have pain? Is the pain sufficiently severe to hinder normal lifestyle? Are there any complications?

What is the functional state of the pancreas?

Patients are classified according to the ABC system[1]

This is a grading system to assess the morbidity of chronic pancreatitis.[1] The proposed grading system takes into account the degree of pain and the presence or absence of diabetes, malabsorption as well as local complications (see table 1).

Table 1. The proposed grading system

A: No pain A0: no diabetes or steatorrhea A1: diabetes mellitus only A2: steatorrhea only A3: Both diabetes and steatorrhea B: Pain present, but no complications B0: no diabetes or steatorrhea B1: diabetes mellitus only B2: steatorrhea only B3: Both diabetes and steatorrhea C: Complications present (pain is usually present but some complications such as biliary obstruction or portal hypertension may be entirely pain free) C0: no diabetes or steatorrhea C1: Diabetes mellitus only C2: Steatorrhea only C3: diabetes mellitus and steatorrhea

Group A patients: Those without pain, or complications, do not warrant treatment except for replacement of pancreatic function, endocrine or exocrine.

Group B patients: Treated with spasmo-analgesics, narcotic analgesics in some, and endoscopy or surgery in those without response to medical treatment and where normal lifestyle is interfered with. Exocrine or

endocrine deficiency is treated on its own merit.

Group C patients: warrant energetic treatment of complications, which may threaten the life of the patient.

Chronic pancreatitis and pancreatic cancer

There have been many reports, which have established the nexus between chronic pancreatitis and cancer[2]. In our experience, pancreatic cancer has never been seen in a patient with chronic pancreatitis due to alcohol abuse. The supervention of cancer in pancreatitis considerably diminishes the outlook of patients with chronic pancreatitis. Most cancers are advanced at the time of diagnosis and treatment is uniformly unsuccessful. Pre-operative identification of cancer is based on the following; (1) CT scan appearance which reveals obvious tumour with vascular invasion (may be fallacious) (2) High CA 19-9 level. (Values above 300 U/ml are 100% specific though only 20% sensitive). Lower values may not be contributory (3) Fine needle cytology and (4)Presence of jaundice in a head mass of levels greater than 5 mg/dl indicate cancer with a sensitivity and specificity of over 90%.The outcome following resection of pancreatic cancer in chronic pancreatitis is poor; the unit policy is to offer surgical resection only to those patients who are strongly motivated to and demand surgical excision. Resection is preceded by counseling and discussion with the patient and his family.In patients without obvious evidence of pancreatic cancer, therapy is more beneficial. The aims of surgical therapy in chronic pancreatitis are; (a) To relieve pain (b)To forestall complications or treat them (c)To preserve functioning pancreatic parenchyma (d) to decrease morbidity and mortality and (e) to preserve quality of life.

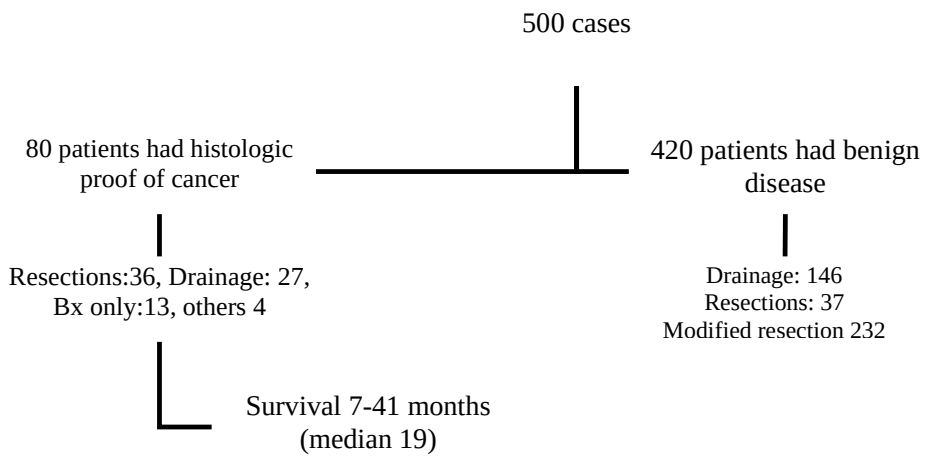
Patient data from our centers

An analysis of the indications, types and results of surgery for the first 500 patients treated in the Unit (1983 to 1997) are presented (see table 2).

Table 2. Indications for surgery

Indication	Number
Intractable pain	457
Pseudocysts/abscesses	58
Inflammatory mass with suspicion of malignancy	92
Biliary obstruction	62
Pancreatic ascites/pleural effusion	19
Others (GI bleed, intestinal obstruction, hollow viscus perforation)	17

Figure 1. Surgeries at our center: a chart



Mortality, morbidity, pain relief and quality of life

Eleven patients died in the postoperative period (mortality 2.6%). Major and minor complications occurred in 17% of cases. Pain relief scores were as follows:

(A) no pain whatsoever: 56% (B) occasional pain (less than once a year and not requiring to report to hospital): 14% (C) Pain frequency once or more per year (out patient): 12% (D) Pain relieved by hospitalization: 13% and (E) unrelieved pain requiring reintervention: 5%

Table 3. Summary of the data from our centers

a) Failures (recurrence of pain) occurred early (within 48 months) and obvious technical factors could be identified.

b) Multivariate analysis identified incomplete stone clearance and absence of ductotomy on to the head as significant causes of recurrent pain and surgical failure[3].

c) Late failures were due to abdominal pain associated with severe fat indigestion (relieved by high dose pancreatic enzymes) or malignancy (4 patients).

d) Patients with resections fared poorly due to pancreatic insufficiency and requirement for expensive, high dose pancreatic enzymes, poor maintenance of body weight and disabling steatorrhea. Although pain was relieved by resection, overall quality of life was poor[4].

e) Head coring combined with lateral drainage provided the best combination of parenchyma preservation with good clearance of stones and strictures in the head region, and this resulted in the best quality of life and pain relief.

f) Patients with intractable pain and normal sized ducts also benefit from drainage procedures with excellent pain relief and quality of life. Resections can thus be avoided[5].

References

1. Ramesh H. Proposal for a new grading system for chronic pancreatitis: the ABC system. J Clin Gastroenterol 2002; 35(1): 67-70
2. Augustine P, Ramesh H. Is tropical pancreatitis premalignant? Am J Gastroenterol 1992; 87(8): 1005-1008
3. Ramesh H, Augustine P. Surgery in tropical pancreatitis: analysis of risk factors. Br J Surg 1992; 79(6): 544-549
4. Ramesh H. Tropical pancreatitis. Indian J. Gastroenterol. 1997: 16:1; 20-25
5. Ramesh H, Jacob G, Lekha V, Venugopal A. Ductal drainage with head coring in chronic pancreatitis with small-duct disease. J Hepatobiliary Pancreat Surg 2003; 10(5): 366-372

Chapter 28

Tropical pancreatitis – Surgical experience at Medical College, Trivandrum

Subhalal N

Summary

***Objective**: To evaluate the clinical presentations, the surgical management and its outcome in tropical pancreatitis (TP).*

***Material and methods**: A retrospective cum prospective analysis of patients with tropical pancreatitis admitted to the Department of Surgical Gastroenterology, Medical College Hospital, Trivandrum (a tertiary level health facility in south Kerala) from January 1993 to September 2004 was carried out. There were 327 cases of tropical pancreatitis during this period. The disease accounted for 9.15% of admissions to the department. Median age of clinical presentation was 34 years (18-65 years). There was a sex predilection for males (M:F = 2.3:3). Of the 327 cases, 189 (57.8%) underwent surgical treatment. One hundred and four cases (55%) were diagnosed to have malignancy and 85 cases were benign on evaluation by various preoperative investigations. Seventy-eight percent had carcinoma of head and the rest of them had carcinoma of the tail of the pancreas. Out of the 81 carcinomas involving the head of pancreas, 32 cases (39.5%) were resectable and underwent pancreaticoduodenectomy. On the contrary, of the 23 cases of carcinoma body and tail of pancreas, only 4 (17.3%) were resectable. Palliative biliary bypass was done in 49 patients with unresectable carcinoma of the head, for relief of obstructive jaundice. Twenty-one cases of unresectable carcinomas underwent nerve ablation procedures for palliation of pain. Of the benign cases, 92% had chronic epigastric pain with radiation to back. The surgical procedures for benign disease were longitudinal pancreaticojejunostomies (LPJ) (70), distal pancreatectomies with splenectomy (9), Frey's procedure (5) and total pancreatectomy (1).*

***Results**: Satisfactory pain relief was attained in 76% of cases of benign tropical pancreatitis. Recurrent pain was noticed in 21% with a latent period ranging from 6 months to 2 years. Incidence of malignancy among patients who underwent longitudinal pancreatico-jejunostomy was 10% with an average latent period of 7 years. All of these were unresectable. Twenty five percent of the patients who underwent biliary bypass alone developed duodenal obstruction later (median interval 4 months) needing gastrojejunostomy.*

Major morbidity rates after pancreaticoduodenectomy were pancreatic leak (6.2%) and delayed gastric emptying (18% after pylorus preserving pancreatoduodenectomies).

Mortality rates were 3.1%, 1.4% and 8% for pancreaticoduodenectomy, LPJ and palliative bypass respectively. Median survivals after resection were 22 months and 7 months for pancreatoduodenectomies and distal pancreatectomies respectively.

***Conclusion**: Carcinoma in tropical pancreatitis has a predilection for the head of pancreas. Pancreaticoduodenectomy appears to improve the survival with acceptable morbidity and mortality rates. Recurrent malignancy after initial resection or bypass is a diagnostic dilemma and majority of these are un-resectable.*

Introduction

Tropical pancreatitis (TP) affects the young: disabling pain, diabetes and the disturbing thought of possible malignant change cripple them at the prime of life. There is definite evidence to suggest that TP is a premalignant condition. This study, from one of the largest tertiary care centers dealing with the disease in this part of the world, attempts to examine the presentations of the disease over the last decade and the outcome of surgical management.

Material and methods

Between January 1993 to September 2004, 327 patients with tropical pancreatitis were admitted to the Department of Surgical Gastroenterology, Medical College Hospital,Trivandrum. These patients were retrospectively analyzed using patient records, operation notes, pathology reports and other documents and also followed up prospectively. TP accounted for 9.15% of admissions to the department in comparison with alcoholic pancreatitis, which accounted for less than 1.5% of the admissions during this period. The median age of clinical presentation was 34 years (18-65 years). Males were affected more often than females (M:F - 2.3:3)

Chronic and recurrent episodes of epigastric pain brought majority of the patients to the clinic. Jaundice with pruritus was the presenting feature in majority of patients who had carcinoma head of pancreas with TP. Fifty eight percent of the TP patients were diabetic, whereas

73% of those with carcinoma in TP were diabetic. Loss of weight was another presenting symptom, which was contributed to by both uncontrolled diabetes and malignant change.

Out of a total of 327 patients, 189 (57.8%) underwent various surgical procedures. Carcinoma of the pancreas was diagnosed in 104 cases (55%) and 85 cases were diagnosed benign by preoperative investigations. Seventy-eight percent of patients had carcinoma in the head of the pancreas while in the rest it was in the body and tail. Out of the 81 carcinomas, 32 involving the head (39.5%) were resectable and underwent pancreaticoduodenectomy (Table1.1). However, out of 23 cases of carcinoma body and tail of pancreas, only 4 (17.3%) were resectable.

Table 1.1: Region of involvement in relation to resectability

Region of involvement	Resectability	Total number
Head of pancreas	32 (39.5%)	81 (78%)
Neck and body of pancreas	2 (13.33%)	15 (14.4%)
Tail of pancreas	2 (25%)	8 (7.6%)

Palliative biliary bypass was done in 49 patients with unresectable carcinoma head of pancreas who presented with obstructive jaundice and intractable pruritus(Table 1.2). Twentyone patients of unresectable carcinomas underwent nerve ablation procedures and celiac ganglion block as palliation for pain.

Table 1.2: Operative procedures

	Sl. No.	Procedures	Total No.
Carcinoma in TP	1	Classical Whipple	10
	2	PPPD	22
	3	Distal pancreatectomy	4
	4	Palliative biliary drainage alone	28
	5	Biliary drainage + GJ	21
	6	Celiac ganglion block/nerve ablation	21
Benign TP	1	LPJ	70
	2	Distal pancreatectomy	9
	3	Frey's procedure	5
	4	Total pancreatectomy	1

Among the benign cases, majority presented with pancreatic pain. Acute presentations in TP can occur infrequently and is a challenge to the surgeon. Two patients presented with haemosuccus pancreaticus, 4 with necrotizing pancreatitis and 12 with pseudocysts (Table1.3).

Table 1.3: Acute presentations in TP

Presentation	No.	%
Pseudocyst	12	3.67
Necrotizing pancreatitis	4	1.2
Pancreatic ascites	3	0.9
Pancreatico-pleural fistula	2	0.6
Haemosuccus pancreaticus	2	0.6

Main pancreatic duct dilatation more than 12 mm by USG or CT scan was noticed in 71% of cases. The surgical procedures for benign disease involved 70 longitudinal pancreaticojejunostomies (Partington-Rochelle

modification of Peustow's procedure), 9 distal pancreatectomies with splenectomy, 5 Frey's procedures and one total pancreatectomy (Table 1.2).

Results

Satisfactory pain relief was attained in 76% of cases of benign tropical pancreatitis after surgery. Recurrent pain was noticed in 21% with a latent period ranging from 6 months to 2 years. Ten percent of those who underwent longitudinal pancreaticojejunostomy developed malignant change with an average latent period of 7 years (median age of occurrence 46 years), all of them had un-resectable disease on re-exploration. Local recurrence of carcinoma after pancreaticoduodenectomy was observed in 1 patient, 5 months after resection. Twenty five percent of the patients who underwent biliary bypass alone developed duodenal obstruction later (median interval - 4 months) needing gastrojejunostomy.

Table 1.4: Complications

Complication	Whipple	PPPD	LPJ	DP	Others	Total No. (%)
Postoperative bleeding	1	1	-	1	2	5 (2.64)
Biliary leak	-	1	-	-	-	1 (0.5)
Pancreatic leak	1 (10)	1 (4.5)	1	-	-	3 (1.5)
Delayed gastric emptying	1 (10)	4 (18)	-	-	-	5 (2.64)
Wound infection	1	2	2	1	5	11 (5.8)
Adhesive obstruction	-	1	3	1	2	7 (3.7)
Portal vein injury	-	1 (4.5)	-	-	-	1 (0.5)
Atelectasis/pneumonia	1	3	5	1	2	12 (6.3)

The morbidities of resection were postoperative bleeding (2.9%), pancreatic leak (6.2%) delayed gastric emptying (18% of pylorus preserving pancreatoduodenectomies), wound infection (5.8%), chest complications in the form of atelectasis or pneumonia (6.3%) and adhesive small bowel obstruction (3.7% -Table1.4)

Table 1.5: Mortality

Procedure	No. of in-hospital deaths	Percentage
Whipple's/PPPD	1	3.1
LPJ	1	1.4
DP	0	-
Others	4	8.16

Mortality rates were 3.1%, 1.4%, 0% and 8% for pancreaticoduodenectomy, LPJ, distal pancreatectomy and palliative bypass respectively (Table 1.5). Multifocal carcinoma was observed in 9% of resected specimens. Longest disease- free survival after Whipple's resection for TP is 6 years. Median survival after resection for carcinoma were 22 months and 7 months for pancreato-duodenectomies and distal pancreatectomies respectively.

Conclusion

Carcinoma in TP has a predilection for the head of pancreas. Multifocal malignancy occurs in 9% of cases. Radial resection appears to confer survival advantage with acceptable morbidity and mortality rates.

Discussion

Kerala has the highest incidence of TP in the world. These patients have coarse pancreatic calcifications as a hallmark of the chronic pancreatitis[4,5]. Tropical pancreatitis occurs in young adults, with male-female ratio of approximately 1.6:1, but as high as 5:1 in some studies.

A number of etiological factors have been implicated. Exogenous toxins

like cyanogenic glycosides linimarin and lotaustralin are contained in cassava and depletion of methionine can cause pancreatitis. Protein calorie malnutrition and deficiency of micronutrients such as selenium, copper, and vitamin A have been implicated as other etiologic factors in TP. Familial clustering of TP has been reported. The role of cassava remains speculative, although a variety of dietary toxins and free radicals and genetic factors appear to be important considerations.

Most of the early TP patients were described as emaciated, ''pot-bellied,'' and edematous with diabetes mellitus. In the early stages of TP, the pancreas may appear totally normal. Later, it becomes atrophic, firm and extremely fibrous. The islets of Langherhans may be spared even in the advanced stages of the disease. A pseudonesidioblastosis is often seen. Diabetic ketoacidosis is distinctly uncommon; however, the diabetes is quite brittle and difficult to control. Diabetes mellitus develops in most of the patients with TP before the age of 30. Pseudocysts are rare even with acute exacerbations and recurrent episodes of pancreatitis. Necrosis of pancreas during acute attack is a rare presentation.

Patients with fibrocalculous changes in the head of the pancreas may experience encasement of the distal bile duct with extrahepatic obstruction and obstructive jaundice. Development of obstructive jaundice, worsening of pain, deterioration of diabetic state and significant weight loss should alert the clinician to the possibility of cancer in TP, as in our experience more than 70% of patients with this combination proved to have carcinoma. Pancreatic exocrine function may be preserved until the very late stages of the TP and clinical steatorrhea is not common. Computed tomography (CT) scanning is very sensitive in diagnosis.

Many retrospective and prospective studies have reported a high association between TP and carcinoma of the pancreas. Previous reports claim that unlike in denovo ductal cancer, which has a distinct predilection for the head, cancer in TP occurs most frequently in the body and tail of the pancreas. However, in our series, 78% of carcinomas occurred in the head of pancreas, with common presenting symptoms of jaundice and pruritus. Earlier studies of surgical management of

carcinoma in TP have reported dismal results after resection and adjuvant therapy. However, current results from our center appear to give good survival advantage for malignancies of the head after resection, although that of body and tail continues to be poor.

Pain is the hallmark symptom of TP. The chronic, relapsing pain often is not controlled by narcotic analgesics. There are reports that octreotide and large doses of high -protease pancreatic enzymes are of significant value in control of pain.

Lateral pancreaticojejunostomy is the most commonly performed operation in patients with fibrostenotic TP. The group with benign TP who underwent LPJ, of whom about 70% had a ductal dilatation more than 12 mm, had effective drainage with symptomatic relief. Do stone clearance and duct enterostomy protect the patient with TP from malignancy? No literature is available on this. There are anecdotal reports of carcinoma occurring several years after a pancreatic drainage procedure. Seventy percent of patients with TP had pain relief after surgery on a ten year follow up. Despite drainage procedures, 10% of cases presented later with inoperable carcinoma of pancreas. The average age for pancreatic cancer onset was 46 years with an average latent period of 7 years, in our series.

In our center, pancreaticoduodenectomy and distal pancreatectomy are the procedures adopted for obvious carcinoma in TP, or in case of a head mass with a strong suspicion of malignancy clinically or radiologically.

Nerve ablation procedures such as celiac ganglion block and splanchnicectomy have been used in the management of malignant pain.

References

1. Pitchumoni CS. Chronic pancreatitis: a historical and clinical sketch of the pancreas and pancreatitis. Gastroenterologist 1998; 6: 24-33.
2. P. Augustine, H. Ramesh. Is tropical pancreatitis premalignant? American Journal of Gastroenterology 1992; 8: 1005-8.
3. Ramesh H. Tropical pancreatitis. Ind J Gastroenterol 1997; 16: 20-25.
4. Geevargheese PJ. Calcific pancreatitis: causes and mechanisms in the tropics compared with those in the subtropics, Trivandrum: St. Joseph's press, 1986: 67-75
5. Petersen, John. Tropical pancreatitis (Liver, Pancreas, and Biliary Disease] Journal of clinical Gastroenterology 2002; 35 (1): 61-66.
6. Thomas PG, Augustine P, Ramesh H, et al. Observations and surgical management of tropical pancreatitis in Kerala and Southern India. World J Surg 1990; 14:32-42
7. Rajan N, Anandakumar M, Abdul Kalam M. Surgery in tropical pancreatitis: review of 64 cases. Kerala Surg J 1995; 2: 7-14.
8. Ramesh H, Augustine P. Surgery in tropical pancreatitis: analysis of risk factors. Br J Surg 1992; 79: 544-9.
9. Chari ST, Mohan V, Pitchumoni CS et al. Risk of pancreatic cancer in tropical calcifying pancreatitis: an epidemiologic study. Pancreas 1994; 9: 62-6.

Chapter 29

Early detection of malignancy in tropical pancreatitis – is it possible?

Sudhindran S, Prasad Krishnan

Summary

Carcinoma of the pancreas is an important cause of death in Kerala. This has been attributed to the high frequency of tropical calcific pancreatitis (TCP) in this part of India. We describe our experience with imaging, biochemical markers as well as the clinical profile of our subjects with pancreatic cancer arising in the setting of previous TCP. In our series, we found that none of the standard investigative modalities were useful in the early detection of cancer in TCP patients. Indeed, despite the prior knowledge of the diagnosis of TCP, which alerts us to the possible development of malignancy in these patients, the timely recognition of malignancy in TCP might prove to be very difficult, as is the case with denovo pancreatic cancers. In future, the increased use of imaging tools such as multi-slice CT scanners and MRI scanners might lead the way towards an earlier and a more precise diagnosis.

Introduction

Carcinoma of pancreas is a leading cause of cancer death in Kerala. This may be partly due to the high frequency of tropical calcific pancreatitis (TCP) in this region, which has now been more or less documented as a premalignant condition [1-3]. Nonetheless, malignancy developing in patients with established TCP is detected at an advanced and incurable stage, that "curative" resection is often not possible. Although overall survival in carcinoma of pancreas may be abysmal, the only realistic approach to long-term survival is complete resection. Accordingly, patients with TCP, a known predisposing factor for pancreatic carcinoma, would be among the first to benefit from early detection of this cancer. The current methods for detection of pancreatic malignancies include biochemical markers such as CA 19-9 and radiological imaging techniques, which are regrettably suboptimal in de novo pancreatic cancers. We looked at the utility of these modalities in the detection of carcinomas occurring in patients with TCP.

Methods

Over a 6 year period from 1999, 61 patients with tropical pancreatitis underwent surgery at Amrita Institute of Medical sciences, Kochi, Kerala.

The indications for surgery was intractable pain (n=46), obstructive jaundice (n=7), gastric outlet obstruction (n=3), leaking pseudocyst (n=1) and suspicion of malignancy (n=4). Over a mean follow up of 30 months (range 4 to 56 months) histologically proven malignancy was detected in 9 patients in this group. The value of serum CA 19-9, occurrence of obstructive jaundice, endoscopic retrograde cholangio pancreatography (ERCP) findings and CT findings were reviewed in patients with and without malignancy (9 and 52 patients respectively) to distinguish any disparity between the two groups that would facilitate early detection of cancer in TCP. Patients with clinically obvious metastatic disease such as presence of supraclavicular or Sister Joseph nodes, peritoneal carcinomatosis on rectal examination, ascites, or radiologic evidence of liver metastasis were excluded from analysis (n=5 patients).

Results

Predictive value of CA 19-9

The mean value of CA 19-9 in patients with proven malignancy was 1086 $\pm$ 846 (range 101 to 1948) as compared to 136 $\pm$ 257 (range 3 to 1408) in those without malignancy. This difference however was not statistically significant (Mann-Whitney U test). The highest value for CA 19-9 that occurred in the benign group was 1408 and was associated with benign biliary stricture and cholangitis. It appears that very high values of CA 19-9, for instance, in excess of 1500, particularly in the absence of jaundice may have a high positive predictive value for malignancy. Below this level, the negative predictive value was much less dependable in this group of patients to rule out malignancy.

Occurrence of obstructive jaundice

Occurrence of obstructive jaundice in patients with known TCP may indicate benign biliary stricture or development of malignancy in the pancreatic head region. In our study 7 patients had developed obstructive jaundice, out of which 3 had malignancies (2 carcinoma of head of pancreas and 1 cholangio carcinoma). The other four patients had benign biliary stricture, due to inflammatory mass in the head of the pancreas. Repeated attempt at endoscopic stenting was unsuccessful

in relieving the jaundice in all four patients with benign strictures and eventually they underwent surgical decompression (whipple-1, Frey's procedure with hepaticojejunostomy-3 patients). Over a mean follow up of 18 months none of these four patients has developed any features to suggest occurrence of malignancy.

The 3 patients with malignant obstructive jaundice were, in fact suspected to have malignancy on CT imaging and 2 had preoperative diagnosis of carcinoma established by CT guided Fine Needle Aspiration Cytology (FNAC). The third patient had malignancy confirmed on frozen section biopsy at surgery. This patient underwent a "curative" resection (Whipple's procedure), whilst the remaining two merely had palliative biliary and gastric bypass, owing to advanced local disease with adjacent vascular invasion. All three have died (within 2 to 14 months), one with liver metastases and the others with malignant cachexia. The longest survivor lived 14 months following the Whipple's procedure.

ERCP findings

ERCP was performed in 31 out of the 61 patients in this study group. The primary indication for ERCP were obstructive jaundice (n=7), suspicion of malignancy (n=4) and in preparation for endotherapy for pancreatic stones in the residual 20 patients. Out of the seven patients with obstructive jaundice, 4 patients had smooth, tapering terminal bile duct strictures appearing "radiologically" benign and underwent initial biliary stenting and subsequent surgical drainage procedure (described above). Remaining three patients had irregular biliary stricture, highly suggestive of malignancy and all three were later histologically proven to have carcinomas (2 adenocarcinoma of pancreatic head and 1 cholangiocarcinoma).

In four patients, where ERCP was done for suspicion of malignancy, there was non visualization of part of the main pancreatic duct. All four were operated and malignancy was detected only in one patient where the ERCP had shown total main pancreatic duct block at the head region without the presence of stones. The other 3 had pancreratic duct blocks due to calculi and had excellent symptomatic relief following duct drainage procedure (Frey's procedure)

On the whole, ERCP findings per se were not entirely diagnostic of malignancies in TCP. Nonetheless, total blockage of pancreatic duct (in the absence of a contributory stone) and irregular bile duct stricture appeared to surface as strong indicators for malignancy in TCP, in this analysis.

CT scan findings

Of the 9 patients with malignancy out of the total 61 in our study group, CT had hinted unresectable pancreatic malignancy in 6 patients. The criteria for advanced malignancy were existence of tumor with peripancreatic extension to contiguous structures such as duodenum or bile duct, vascular encasement or invasion (such as to superior mesenteric vessels or inferior vena cava), and local lymphadenopathy. The remaining 3 patients with proven malignancy did have CT evidence of a pancreatic head mass but were deemed to be more likely to be of inflammatory origin rather than a malignant tumour. This was primarily due to the existence of extensive intraductal calcification, predominantly in the head region, making CT distinction of malignancy particularly demanding in this group. Splenic vein thrombosis was observed in 7 patients in our series and was not a sign of malignancy. This probably occurred following an acute exacerbation of chronic pancreatitis.

In the benign group of patients (n=52), CT had shown head mass in 11 patients. The radiologic features which tended to differentiate these from a carcinoma were presence peripancreatic inflammatory changes, the occurrence of unhindered ductal dilatation all the way to the tail region, calcification in the mass and absence of perivascular involvement. Nonetheless, the differential diagnosis by the radiologist in these 11 cases included malignancy. All have been operated and hitherto followed for a mean of 17 months (4 to 51 months) with no signs of malignancy emerging to date.

Discussion

We found that, regardless of the tests used, whether biochemical or radiological, distinguishing between an inflammatory and neoplastic mass in TCP was challenging. CA 19-9, the only widely used tumor

marker, is of limited value as a screening tool, because approximately 10% to 15% of individuals do not secrete CA 19-9 due to their Lewis antigen status [4]. Additionally, CA 19-9 levels may be within the normal range while the cancer is still at a small and asymptomatic stage and often is elevated in benign biliary or pancreatic conditions, such as acute cholangitis or chronic pancreatitis [5, 6]. In our study too, the value of CA 19-9 inclined to be of significance only in cases where it was above 1500 units. Indeed, in two benign cases with obstructive jaundice and cholangitis, values in the region of 1000 were observed. There is a growing field of research to discover new biomarkers of pancreatic cancer. A better knowledge of the most frequent genetic alterations, and the most frequently up-regulated proteins specifically found in pancreatic cancer would hopefully provide the basis for developing sensitive tumour markers for this malignancy.

Development of obstructive jaundice in patients with TCP, though often signaled a malignant transformation, was not a definite omen of pancreatic cancer in our series. Benign biliary stricture occurred with equivalent regularity and almost consistently required surgical decompression of the bile duct. Neither the depth of jaundice nor levels of alkaline phosphatase were contributory in this regard.

Among the imaging modalities, CT scan was much more valuable at predicting malignancy than ERCP. We were unable to characterize an ERCP finding that could reliably imply the presence of malignancy. Perhaps the only sign that may be of possible benefit in this respect maybe total blockade of the main pancreatic duct in the absence of an incriminating stone (or duct penetrating sign)[7]. CT scan, on the other hand showed several signs to distinguish malignant head masses in TCP; involvement of fat planes around the vascular structures, particularly the superior mesenteric artery, peripancreatic extension of the mass to contiguous structures such as duodenum, local lymphadenopathy and absence of peripancreatic inflammatory changes or calcification in the mass. Regrettably, existence of these signs indicates inoperability in the great majority of cases and do not aid us in the early detection of this dreadful ailment.

Thus, none of the standard investigative modalities that we studied were

useful in the early delineation of cancer in TCP patients. As a matter of fact, timely recognition of malignancy in TCP, despite its reputation as a pre malignant entity, may prove to be much more difficult than denovo pancreatic cancers. State-of-the art- techniques such as multi-slice CT scanners and MRI scanners may ultimately lead us to the light at the end of the tunnel.

References

1. Whitcomb DC. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. Am J Physiol Gastrointest Liver Physiol 2004; 287:G315-9.
2. Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. Pancreas 1994; 9:62-6.
3. Augustine P, Ramesh H. Is tropical pancreatitis premalignant? Am J Gastroenterol 1992; 87:1005-8.
4. Abrams RA GL, Chakravarthy A, Sohn TA, Zahurak ML, Haulk TL, et al. Intensified adjuvant therapy for pancreatic and periampullary adenocarcinoma: survival results and observations regarding patterns of failure, radiotherapy dose and CA19-9 levels. Int J Radiat Oncol Biol Phys 1999; 44:1039-46.
5. Furuya N KS, Hasebe O, Tokoo M, Mukawa K, Maejima S, et al. Comparative study of CA242 and CA19–9 in chronic pancreatitis. Br J Cancer 1996; 73:372-6.
6. Ritts RE PH. CA 19-9 in pancreatic cancer. Surg Oncol Clin N Am 1998; 7:93-101.
7. Ichikawa T, Sou H, Araki T, Arbab AS, Yoshikawa T, Ishigame K, Haradome H, Hachiya J. Duct-penetrating sign at MRCP: usefulness for differentiating inflammatory pancreatic mass from pancreatic carcinomas. Radiology 2001; 221:107-16.

The Indian Pancreatitis Study Group has a mission - to study the etiology of pancreatitis in india. This might also help gain insights into the pathogenesis of the disease elsewhere. We wish to use the knowledge thus obtained to bring down the incidence of pancreatitis and to prevent it wherever possible. Hard task, but we shall do it.

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