Comparative Study of the Clinical Profiles of Alcoholic Chronic Pancreatitis and Tropical Chronic Pancreatitis in Tamil Nadu, South India


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Summary: In a comparative study of tropical chronic pancreatitis (TCP) and alcoholic chronic pancreatitis (ACP) occurring in the same population, we analyzed the clinical profile of 50 patients of ACP seen over the past 3 years at our centers and compared this with the profile of our TCP patients. A majority (75%) of patients in both groups belonged to Tamil Nadu and 90% had never consumed cassava. Whereas TCP occurred in young subjects of both sexes, ACP patients were all males and presented at an older age. The frequency of pain, diabetes, and pancreatic calcification was similar in the two groups. Patients in both groups were lean, but signs of severe malnutrition were rare. Prediabetic patients had normal body mass index. There were striking differences in radiological appearance of pancreatic calculi in TCP and ACP. Malignancy of the pancreas was present in three patients with TCP. Benign bile duct stenosis was seen in three patients with ACP but not in TCP. Compared to ACP seen in the West, our ACP patients had a shorter duration of symptoms in spite of having advanced disease. TCP and ACP have distinct clinical profiles and it is possible that some environmental factors may hasten the progress of ACP in the tropics. Key Words: Tropical chronic pancreatitis—Alcoholic chronic pancreatitis.

Chronic alcohol abuse is the most common cause of chronic calcifying pancreatitis (CCP) in the West (1). The highest reported frequency of CCP is in southern India where an idiopathic, nonalcoholic form of CCP, referred to as tropical chronic pancreatitis (TCP) has been described (2). We and others have reported on the clinical features of TCP (3–5). Alcoholic chronic pancreatitis (ACP) is reported to be uncommon in Kerala (6), although it is the most common cause of CCP in North India (7).

This study is a retrospective analysis of proven cases of CCP seen at our centers. The aim of this study was to emphasize the existence of ACP in South India and to compare the profiles of ACP and TCP seen at our centers.

MATERIALS AND METHODS

A total of 209 patients were diagnosed at our centers to have CCP between January, 1987 and December, 1989.
Diagnostic criteria

**Chronic calcifying pancreatitis (CCP)**

Patients who had one or more of the following criteria were diagnosed to have CCP.

- Pancreatic calculi seen on plain x-ray of the abdomen confirmed by ultrasoundogram. Of CCP patients, 87% had pancreatic calcification.
- Endoscopic retrograde cholangiopancreatography (ERCP) showing features suggestive of chronic pancreatitis (CP) as defined by Cambridge criteria (8). Thirty-one patients had ERCP evidence of CP.
- Recurrent abdominal pain suggestive of pancreatitis with ultrasonographic features of CP (9) with pancreatic exocrine insufficiency (fetal chymotrypsin value <5.8 U/g) (10). These criteria were used to diagnose CCP in 10 patients (five TCP, two ACP, three others).

**Alcoholic chronic pancreatitis (ACP)**

ACP patients giving a history of consumption of at least 50 g of alcohol per day for at least 5 years prior to the onset of symptoms were diagnosed to have ACP. Fifty patients who fulfilled these criteria were included in the study. Nine other patients who regularly consumed alcohol but whose duration of alcohol abuse was <5 years prior to the onset of symptoms (pain or diabetes) were excluded from the study.

**Tropical chronic pancreatitis (TCP)**

TCP patients who had no known cause of CP (like alcoholism, hypercalcemia, or gall stone disease) were diagnosed to have TCP. Of patients seen during this period, 150 had TCP.

A detailed history was taken and a thorough physical examination carried out in all patients diagnosed to have CCP. Special attention was given to the state of domicile of patient, dietary history of cassava consumption, duration of alcohol abuse, and age at onset of various symptoms.

On examination, signs of malnutrition and features of chronic liver disease were carefully looked for.

Imaging techniques

**A plain x-ray of the abdomen**

After proper preparation, a plain x-ray of the abdomen was taken in all patients and carefully screened for presence of calcification in the region of the pancreas.

An ultrasonographic examination

An ultrasonogram was carried out in 26 ACP and 90 TCP patients by a method described earlier (11) specifically to look for contour and size of pancreas, echogenicity of parenchyma, ductal size and contour, and calculi.

**Endoscopic retrograde cholangiopancreatography (ERCP)**

ERCP was performed in 29 TCP patients and 9 ACP patients. The pancreatic duct changes were classified according to Cambridge criteria (8).

Biochemical investigations

**Glucose tolerance test (GTT) and glycosylated hemoglobin**

A 75-gm GTT was carried out in all patients and abnormalities classified according to World Health Organization criteria (12). Plasma glucose was estimated by Hitachi Autoanalyser using glucose oxidase method (Boehringer Mannheim, West Germany). Glycosylated hemoglobin was estimated by colorimetric method of Eross et al. (13).

**Fecal chymotrypsin assay (FCT)**

FCT was carried out by the spectrophotometric method of Kasper and Neumann (14) to assess pancreatic exocrine function in 60 TCP patients and 26 ACP patients. An FCT value of <5.8 U/g (mean - 2 SD of control value) was taken as evidence of pancreatic insufficiency (10).

Statistical analysis

All values are expressed as mean ± SD. Clinical and biochemical parameters were compared using t-test.

RESULTS

Table 1 gives the clinical and biochemical features of TCP and ACP.

State of origin

The majority (75%) of patients came from our own state of Tamil Nadu, 12% from Andhra Pradesh, 8% from Kerala, 2% from Karnataka, and 3% from other parts of the country. This distribution was similar in the two groups.

History of consumption of cassava

Only patients belonging to Kerala gave history of consumption of cassava. Even among these patients none consumed it as a staple diet, five pa-
patients consumed it occasionally (less than three times a week) and three others consumed it rarely (less than twice a month).

History of alcohol consumption
All but seven of the TCP patients were strict teetotallers. These seven patients consumed alcohol not more than once in a fortnight. In the ACP group, mean duration of alcohol consumption was 14 ± 7.9 years.

Sex distribution
All ACP patients were males. In the TCP group, males outnumbered females with a male to female ratio 2.5:1.

Age at presentation
TCP patients were, on an average, a decade younger than ACP patients.

Abdominal pain
The frequency of pain in the abdomen was similar in the two groups—86% in ACP and 82% in TCP. However, the age at onset of abdominal pain was significantly lower in TCP than in ACP patients. Also, the duration of pain prior to presentation was longer in TCP than in ACP.

Diabetes mellitus
The prevalence of overt diabetes at the time of presentation was similar in the two groups—84% in ACP, 78% in TCP. TCP patients developed diabetes at an earlier age compared to ACP patients. The duration of diabetes was, however, similar in the two groups. The fasting and postprandial blood sugar levels in ACP patients were comparable to those of TCP patients.

Steatorrhea
A history of steatorrhea was obtained in 25% of patients in the two groups. However, as discussed later, pancreatic exocrine insufficiency diagnosed by low fecal chymotrypsin value was present in a much higher percentage of patients in both groups.

Pancreatic calcification
The frequency of pancreatic calcification was similar in the two groups—90% in ACP and 84% in TCP. However, the radiological appearance of calcification in TCP differed markedly from that seen in ACP. The calcification in TCP were typically large (>10 mm), dense, and discrete with well circumscribed margins, whereas the calcification in ACP were characteristically agglomerates of small, speckled calcification with hazy margins.

ERCP
Of the 29 TCP patients in whom ERCP was done, pancreatic duct was visualized in 23 and bile duct in 20. Of the nine ACP patients, pancreatic duct was seen in eight and the bile duct in seven. None of the patients had congenital anomalies like pancreas divisum or annular pancreas. In four TCP patients the pancreatic duct could not be filled beyond the head region due to large intraductal calcification in the head. All patients, both ACP and TCP, showed moderate to severe changes on ERCP. None had normal or minimal changes. Benign bile duct stenosis was seen in three patients with ACP. None of these three patients had clinical, ultrasonographic, or ERCP evidence of malignancy. Two TCP patients had bile duct obstruction and both had pancreatic head malignancy. None of the TCP patients had benign bile duct stenosis.

Ultrasonography
Ultrasonography in TCP showed shrunken pancreas, increased parenchymal echogenicity, and dilated pancreatic duct with intraductal calcification. The majority of patients with ACP showed similar findings but in 20% of patients the pancreas was enlarged. In 40% of patients with ACP the calcification was detected in the parenchyma of the pancreas rather than within the pancreatic duct.

Fecal chymotrypsin assay
Pancreatic exocrine insufficiency was seen in 81% of TCP and 86% ACP patients tested.
Nutritional status and body mass index (BMI)

These were comparable in the two groups. The majority of ACP and TCP patients with diabetes were lean and gave history of significant weight loss after onset of diabetes. Premorbid BMI calculated on the basis of patient's recall of earlier weight revealed that patients had normal BMI prior to onset of diabetes. Also, nondiabetic patients had normal BMI. Signs of extreme malnutrition like pedal edema, pot belly, parotid enlargement, and dermatological changes were seen in only 5% of patients in both ACP and TCP patients.

Evidence of chronic liver disease

Two patients with ACP had evidence of cirrhosis of the liver with decompensation. They had pedal edema, jaundice, and ascites with ultrasonographic features of shrunken liver and splenomegaly. Ascitic fluid amylase was not elevated. None of the TCP patients had overt evidence of chronic liver disease.

Evidence of pancreatic malignancy

Three patients with TCP, two males and one female, had pancreatic malignancy. The mean age of patients with pancreatic malignancy was 59 years. Two of them presented with obstructive jaundice and the third with mass in the abdomen. ERCP in two patients showed dilated biliary tree and evidence of stricture of the lower end of the common bile duct. The two patients with obstructive jaundice underwent surgery where the diagnosis was confirmed. None of the ACP patients had any evidence of pancreatic malignancy.

Table 2 compares the clinical profile of ACP seen at our center with that of ACP reported in different series from affluent, westernized countries (15–18).

**DISCUSSION**

The subject of TCP in South India has been extensively reviewed (3–6). There are, however, few reports of ACP from South India. This is of interest because TCP has the highest known frequency in South India. In this paper we report on the clinical profiles of these two forms of CCP occurring in the same population. This comparison of TCP and ACP brings out some interesting facts—some new and some well established.

The profile of TCP described by us is essentially similar to that described earlier from Kerala (3,19). It is an idiopathic, nonalcoholic painful, chronic calcific pancreatitis occurring in young patients of both sexes, a majority of whom by the time of diagnosis have features of advanced CP. The conspicuous difference is that none of our patients consumed cassava as a staple diet; in fact it was only in the patients from Kerala that we could elicit any history of cassava consumption.

In hospital-based studies on TCP, male preponderance has been observed—a male to female ratio of 1.6:1 in Kerala (19,6) and 2.5:1 in our study. Balaji (2) studied hospital admissions for TCP and conducted a field study to detect TCP in an area of high

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<thead>
<tr>
<th>Table 2. Comparison of the profile of ACP seen in Tamil Nadu with that of ACP in westernized countries</th>
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<tbody>
<tr>
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<tr>
<td><strong>ACP in</strong>                  </td>
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<tr>
<td>Percentage of ACP</td>
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<tr>
<td>patients in the series</td>
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<tr>
<td>Sex ratio (M:F)</td>
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<tr>
<td>Mean age at diagnosis (years)</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
</tr>
<tr>
<td>Frequency (%) of Abdominal pain</td>
</tr>
<tr>
<td>Calculated</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td>Severe exocrine insufficiency</td>
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* Data of 100 ACP cases with pancreatic calcification.
* Data at entry into follow-up study.
* Median age at diagnosis.

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prevalence in Kerala. Although the hospital data showed male predominance, in his population study he found female predominance (M:F ratio of 1:1.8). He suggests that this could be because women in India often do not seek medical attention and therefore do not appear in hospital records.

The profile of TCP not only in Tamil Nadu but also in Kerala appears to be gradually changing. Geevarghese in his 1968 monogram (19) gave the classic description of the natural history of the disease—pain in the abdomen in childhood, diabetes by puberty, and death at the prime of life. Today's patients appear to be older and have greater life expectancy than their counterparts of two decades ago. The mean age at onset of the disease in our series of 22.9 years is similar to 20.7 years reported by Balakrishnan in his recent review of TCP (6) and 23.9 years in the field study conducted in Balaji (2). Similarly, the age at presentation of 32.6 years in our study is similar to 32.8 years in Balaji's study (2). Extreme emaciation, potbelly, pedal edema, and cyanotic hue of the lips—the characteristic features of the patients from Kerala—were uncommon in our patients. Balaji in his study (2) observed that whereas his patients were undernourished by the Indian Council of Medical Research standards, their nutritional status was comparable to that of the control population. Cirrhosis has been reported in 12–48% of patients in TCP (6,19). Overt liver cirrhosis was not seen in any of our patients. With the improvement in living conditions, better nutritional status, and greater availability of medical facilities, TCP appears to be running a less aggressive course today. This was predicted by Geevarghese in his 1985 monograph (4).

The etiology of TCP remains elusive. Chronic exposure to cyanide, cassava in Kerala, and cigarette smoke in the West, has been implicated as an etiological agent of CCP (20). The presence of TCP in areas where cassava is not consumed raises the possibility that there may be some, as yet unidentified, cyanogens in the diet of our population. Rubber seed oil, an extract of rubber seed, is normally discarded but is being used to adulterate groundnut oil—the commonly used cooking medium. Rubber seed oil has been shown to have high cyanogen content and merits further study to establish its pathogenic role in pancreatic disease in Tamil Nadu (21). Similarly, kerosene fumes, choolah smoke, and other xenobiotics have been suspected to play a role in inducing pancreatic damage in our population (22). However, well designed case controlled studies are necessary to conclusively establish their role in the causation of CCP.

In an area where the predominant form of CCP seen is of the nonalcoholic variety, it is difficult to set minimum criteria for defining ACP. The study by Durbec and Sarles (23) has shown that there is no threshold for alcohol toxicity and that there is progressively increasing risk of development of ACP with increasing alcohol intake. Although in a retrospective study it would be difficult to differentiate modest from heavy alcohol abuse, we have used consistent alcohol abuse for at least 5 years prior to onset of symptoms as the criterion for exclusion of CCP patients into the ACP group. This has also been used by authors in the West (15–18,24). Classification of patients with shorter duration of alcohol abuse poses a problem. We have excluded the nine male patients with such history from the study. Some of these could have been TCP patients with incidental history of alcohol abuse. It is also possible that some could have been ACP patients who, in the presence of other environmental toxins, may have developed ACP with a shorter duration of alcohol abuse. Until specific markers for ACP and TCP are available, the problem of classifying this group of patients will remain unresolved.

ACP seen at our centers differs in certain respects from that described in the West (15–18,24). Although ACP is the etiology in 60–70% of patients with CP in the various series from the West, it could be implicated in only 25% of our patients. ACP in females is being increasingly reported from the West reflecting increasing incidence of alcoholism in females. In India, alcohol abuse in women is considered a social taboo and therefore alcoholism and alcohol-induced diseases are uncommon in women.

The incidence of features of advanced CP (diabetes, calcification, and severe exocrine insufficiency) is very high in our series of ACP patients with 90% having calcification. Due to nonavailability of more sensitive tests of exocrine function like the Secretin test, patients with less severe disease may have been missed. Referral bias could also have contributed to this as 65% of the ACP patients, all diabetics, were diagnosed at the Diabetes Center. Therefore, prevalence rates of diabetes in CCP in our study should be interpreted with caution. In an earlier study, we have demonstrated the usefulness of fecal chymotrypsin assay in differentiating pancreatic from primary forms of diabetes (10). In that study we have shown that in TCP there is a very
high incidence of pancreatic insufficiency. In the present study we have found that in ACP, 86% of patients had exocrine insufficiency. This is not surprising, as a majority of our ACP patients had other features of advanced disease as well.

However, what is more interesting is the observation that even in patients with advanced disease the duration of symptoms was remarkably short. In ACP in the West the mean duration of symptoms prior to development of calculi is 8 years (25). The mean duration of symptoms in our patients with calculi was 4 years. This is significantly shorter than the duration of symptoms in TCP as well. Could it be that the pancreaticototoxic environmental factors postulated to cause TCP accelerate the progress of ACP in the tropics? The similar duration of diabetes in the TCP and ACP suggests that with the onset of diabetes and consequent weight loss, the patients tend to seek medical attention.

It appears that TCP and ACP are two distinct forms of CCP with striking differences in their clinical profile. TCP occurs in young, nonalcoholic subjects of both sexes. ACP patients, all males in our study, give a long history of alcohol abuse and present at an older age. The radiological features of calculi in TCP and ACP are so characteristic that often the nature of CCP can be predicted by seeing the plain x-ray of the abdomen alone.

Ultrasoundographically, in TCP, the gland is shrunken and fibrosed with dilated pancreatic duct and intraductal calculi (11). In the present study, we found that the ultrasonographic features of TCP and ACP were similar. This could be because most ACP patients had advanced disease. However, enlargement of the gland was noted in some cases of ACP as has been reported in the West (9). This does not occur in TCP where there is conspicuous paucity of acute inflammatory changes on histopathology (26).

Pancreatographic appearances of TCP and ACP were similar in our study as well as in the Balakrishnan et al. study (27). Ghevarghese (19) postulated that pancreatic duct abnormalities leading to proximal pancreatic duct obstruction may predispose patients to develop pancreatitis. In our patients we did not find any evidence on ERCP to substantiate this hypothesis. However, interesting differences were noted in the bile duct changes seen on ERCP in TCP and ACP. Benign bile duct stenosis, reported to occur in 5–10% of patients with ACP (28), was observed by us in three ACP patients. This was not seen in TCP patients. Peripancreatic fibrosis, known to result from recurrent bouts of acute inflammation in ACP can lead to benign strictures of the adjacent intestine and bile duct and produce thrombosis of the splenic vein. These have not been reported in TCP.

There are increasing reports of pancreatic malignancy supervening on TCP (29,30,31). Lowenfeld et al. (30) study of risk of development of pancreatic cancer in various forms of CCP found that TCP patients were at the highest risk of developing pancreatic carcinoma. TCP patients developing pancreatic malignancy are generally between 40 and 60 years of age suggesting that with increasing longevity of TCP patients this complication is likely to be seen more often in the future.

REFERENCES