Tropical Gastroenterology 2020;41(2):60-65

Original Article

Idiopathic Chronic Pancreatitis in Bihar: A Perspective from Eastern India

Utpal Anand[1], Ramesh Kumar[2], Rajeev Nayan Priyadarshi[3], Bindey Kumar[4], Sanjay Kumar[5], Kunal Parasar[1]

[1]Department of Surgical Gastroenterology, AIIMS, Patna, Bihar, India. [2]Department of Gastroenterology, AIIMS, Patna, Bihar, India. [3]Department of Radiodiagnosis, AIIMS, Patna, Bihar, India. [4]Department of Paediatric Surgery, AIIMS, Patna, Bihar, India. [5]Department of Surgical Gastroenterology, IGIMS, Patna, Bihar, India.

Corresponding Author: *Dr Utpal Anand*
Email: utpalanand2@gmail.com, drutpalanand@aiimspatna.org

ABSTRACT

Background: There is a lack of data describing the clinical profile, complications, and treatment outcome of patients with idiopathic chronic pancreatitis (ICP) from Eastern India. The current study aimed to present data on these aspects from a tertiary care centre of Bihar - a part of Eastern India.

Methods: Prospective data were collected with regard to clinic-epidemiological profile, complication, and treatment outcome from each patient of ICP (n=129). The median follow-up period was 3.8 (01 - 06) years.

Results: ICP constituted the most common (64.1%, 129/201) cause of chronic pancreatitis. The mean age ± SD of ICP patients was 31.5 ± 11.2 years, and 71 (55%) were male. Diabetes and symptomatic steatorrhea were found in 25% (n=33) and 6.2% (n=08) patients. Pancreatic head mass was found in 43 (33%) patients, of which 17 (39.5%) was malignant. When patients were categorized into early-onset (= 30 years) and late-onset (>30 years) groups, no significant difference was found with regard to the proportion of patients with diabetes, head mass, and malignancy. The majority (69.7%) of patients required surgery (Frey's procedure) due to failed medical therapy. Seventy-four (82%) patients had significant pain relief during a median follow-up of 3.8 years after surgery.

Conclusions: ICP is the most common cause of chronic pancreatitis in Bihar. The majority of such patients are young, with slight male preponderance. They have a significant risk of developing diabetes and pancreatic malignancy. They are poorly responsive to medical therapy, and the outcome of surgical therapy is good.

KEYWORDS: Chronic pancreatitis, Tropical pancreatitis, Idiopathic chronic pancreatitis.

Introduction

Chronic pancreatitis (CP) is a condition characterized by irreversible destruction and fibrosis of the pancreatic parenchyma, which may lead to exocrine and endocrine pancreatic insufficiency.[1] Alcohol is the most common cause of CP worldwide. A large proportion of patients with CP have no identifiable cause, which has been called idiopathic chronic pancreatitis (ICP). Though still controversial, ICP includes several well-described disease subgroups like early and late-onset ICP, tropical CP (TCP), minimal change CP, and small duct CP.[2-5] In earlier reports, mostly from south India, TCP was used synonymously with ICP and was reported to be the most common form. The characteristic features described for TCP was younger age at onset, presence of large intraductal calculi, and an accelerated course of the disease leading to diabetes and steatorrhea, and a high susceptibility to pancreatic cancer.[6-11] A prospective multicentre survey from centres located both in the north and south India involving 1086 subjects reported that only about 3.8 % to 5.8 % of patients could fulfil the criteria of TCP, and ICP was the most common form of CP in India (622; 60.2% patients).[12]

Studies from South India have also revealed a changing trend of TCP.[13] Data from Northern India is variable and show overlapping pictures of ICP and TCP.[14] There is a lack of detailed studies of ICP from Eastern and Western India. This study aims to present the clinic-epidemiological profiles, complications, treatment, and outcome of ICP patients from Bihar, which is a part of Eastern India.

Material and Methods

This study is a retrospective analysis of prospectively collected data from the Department of Surgical Gastroenterology at Indira Gandhi Institute of Medical Sciences, Patna, India, between January 2011 and July 2017. Two hundred and one patients with CP were referred for surgical evaluation, of which 129 patients had ICP, which constituted the core group of our study. Alcoholic CP (n=66), hyperparathyroidism (n=4), and pancreatic divisum (n=2) were the other aetiologies excluded from the study.

The diagnosis of CP was based on the presence of pancreatic calculi, ductal dilatation and parenchyma atrophy on Ultrasonography, Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI), Magnetic Resonance Cholangiopancreatography (MRCP) or Endoscopic ultrasound (EUS) whenever required. ICP was diagnosed in patients with CP by excluding patients with significant alcohol consumption and other potential causes. The patients with ICP were divided into early-onset and late-onset ICP depending on the age of onset of symptoms (before or after 30 years). Alcoholic CP was considered when alcohol intake exceeded 80 g/day for males or 60 g/day for females for at least two years in the absence of other causes.[15] Autoimmune CP was diagnosed by the International Consensus Diagnostic Criteria (ICDC) published in 2011.[16] The investigations for this included imaging (US/CT or MRI), blood test (serum IgG4 levels), and EUS guided core biopsy. Response to steroid therapy was also taken into account. Metabolic CP was diagnosed if there was evidence of hyperparathyroidism or hypertriglyceridemia. However, patients with AIP and Metabolic CP were excluded from our study. Diabetes was diagnosed if the fasting plasma glucose value was equal to, or greater than, 126 mg/dL confirmed on two occasions and a plasma glucose value equal to, or greater than, 200 mg/dL after a two-hour glucose load confirmed on two occasions, and requirements for insulin or oral hypoglycaemic drugs. A qualitative faecal microscopic examination (using Sudan stain) was done in all patients. A 72 hours faecal fat estimation was done in patients with a clinical suspicion of steatorrhea or when the microscopic test was positive. Nutritional status was assessed using WHO growth charts for height for age and body mass index (BMI) for age.

A detailed clinical history and examinations were made in all patients. Baseline routine investigations such as complete blood count, liver function test, kidney function tests, blood glucose, stool for fat, and another test as and when needed were done in all patients. Radiological investigations included abdominal ultrasonography & abdominal CT scans in all cases, and MRI with MRCP or EUS whenever required. After obtaining consent from each patient, data on demography, clinical profiles, radiological characteristics, complications, management, and therapeutic responses were collected for analysis.

Statistical Analysis

The continuous variables with normal distribution were expressed as mean (SD), and those with skewed distribution were expressed as median (range). Categorical data were presented as proportions. Comparisons for continuous variables were made with student t-test or Mann Whitney test whenever applicable. Comparisons for categorical variables were made using Chi-square or Fisher's test, wherever applicable. A P value <0.05 was taken as significant. Data were analysed using GNU PSPP Statistical analysis software.

Results

Epidemiology

ICP constituted the most common (64.1%, 129 of 201) cause of CP in Bihar. The ICP patients (n=129) were uniformly distributed across the state, and there were no high-density pockets. The mean age ± SD of patients was 31.5 ± 11.2 years (range: 11-65 years). Seventy-one (55%) patients were male, and the male-female ratio was 1.2:1. When patients were categorized into two groups according to the onset of symptoms before or after 30 years of age, the mean age of the patients in early-onset (before 30 years, n = 73) and late-onset (after 30 years, n= 56) groups were 23.5± 5 years and 41.8± 8.3 years, respectively.

Clinical Profiles

The mean duration of symptoms at the time of presentation in patients with ICP was 40.2 months. Abdominal pain (95%) was the most frequent presenting symptom in both early and late-onset ICP (73/73; 100% vs. 50/56; 89%). The pain was moderately severe, with long pain-free intervals in between. The BMI was similar between patients with early and late-onset ICP (20.7 ± 3.6kg/m^2 vs. 20.2 ± 3.5kg/m^2). Jaundice was the presenting complaint in 12.4% (16/129) patients. The cause of jaundice was biliary obstruction due to pancreatic malignancy, common bile duct (CBD) stones, and CBD stricture in 7, 2, and 7 patients, respectively. Pseudopancreatic cysts in the pancreatic head were present in 7.75% (10/129) patients.

Pancreatic Ducts and Calcification

The central pancreatic duct was markedly dilated in most patients with median (range) size being 8 (3 - 40) mm. The ductal dilatation was similar between early and late-onset groups (8.8 mm vs. 8.0 mm, p=0.19). All ICP patients had pancreatic calcification and diffuse parenchymal atrophy. The pattern of pancreatic calcification was similar between two groups, and in the majority, multiple large intraductal were seen throughout the duct.

Endocrine and Exocrine Insufficiency

Diabetes was detected in 25% (33/129) of ICP patients, and its prevalence was similar between early and late-onset ICP (21.9% vs. 30.3%, P=0.31). Twelve of 33 diabetic patients required insulin therapy for blood sugar control. None of them had microvascular or macrovascular complications related to diabetes. Four of 33 diabetic ICP patients fitted into criteria of fibrocalculus pancreatic diabetes (FCPD), i.e., the patient had diabetes for more than ten years; later diagnosed chronic pancreatitis on evaluation for pain abdomen. Steatorrhea was noted in 8 (6.2%) patients with ICP.

Pancreatic Head Mass and Malignancy

On radiological investigations, the pancreatic head mass was found in 33% (43 of 129) patients. Cytological examination revealed adenocarcinoma in 39.5% (17 of 43) patients with head mass and overall 13% (17 of 129). The proportion of malignancy was similar between patients with early and late-onset ICP (n= 9; 12.3% vs. N=8; 14.2%, p=0.79) (**Table 1**). Twelve out of 17 (70%) patients with pancreatic adenocarcinoma were locally advanced with encasement of the portal vein with evidence of portal hypertension.

Table 1: Comparison of Early and late onset Idiopathic chronic pancreatitis (ICP).

Age of onset of ICP	Early onset ICP (n=73)	Late onset ICP (n=56)	P value
Head Mass	24 (32.8%)	19 (33.9%)	1.00
Malignancy	09 (12.3%)	08 (14.2%)	0.79
Diabetes	16 (21.9%)	17 (30.3%)	0.31
Pancreatic duct mean in mm (SD)	8.8 (4.2)	8.0 (2.6)	0.19

Surgical Treatment and Outcome

All patients initially received medical therapy in the form of pancreatic enzyme supplementation, low dose opioids, and antioxidants. However, 90 (69.7%) patients required surgery due to severe and recurrent pain refractory to medical therapy or complications of chronic pancreatitis. Head coring with lateral pancreaticojejunostomy. (Frey's procedure) was done in all patients who required surgery. The average operative time was 3.0± 0.5 hours, and the average blood loss during the operation was 500 ± 215 mL. There was no pancreaticojejunostomy leak and postoperative mortality. The median (range) follow-up period post-surgery was 3.8 (01 - 06) years. Seventy-four (82%) patients had significant pain relief until the last follow-up. Insulin requirement reduced in 8 patients who required a high dose of insulin preoperatively.

Discussion

Our study revealed that ICP was the most common cause of CP in Bihar. The most common age of presentation was the third and fourth decades of life with slight male preponderance. Abdominal pain was the most common presenting symptom. The prevalence of diabetes among ICP patients was reasonably common, while steatorrhea and malnutrition were uncommon. With regards to complications, a head mass was seen in 1/3rd cases, pseudocyst was rare, and the malignancy rate was high in both early and late-onset ICP. The response to medical therapy was generally poor in such patients, and the outcome of surgical therapy was good.

Based on the age of the presentation, layer *et al*.[17] from the Mayo Clinic (USA) first described two clinical patterns of ICP, i.e., early- and late-onset pancreatitis. They observed early-onset ICP had more frequent and severe pain but less calcification, endocrine and exocrine insufficiency in comparison to late-onset ICP. However, in contrast to western reports, a study from North India by Garg *et al*.[18] reported continuous pain, large pancreatic calculi, and predominantly large duct disease in early-onset CP resembling TP. Patients with late-onset CP had recurrent episodes of pain, less frequent pancreatic calcification, and predominantly had small duct disease resembling ICP as described from Western countries. A study from Kerala (South India) by Rajesh *et al*.[19] revealed a higher incidence of endocrine and exocrine insufficiency with late-onset ICP in comparison to early-onset ICP. The risk of pancreatic carcinoma or the development of pseudocyst was equal in both groups. Our study failed to find any difference in clinical presentation, phenotypic characteristics, diabetes, and risk of malignancy between early and late-onset ICP.

The natural history of TCP earlier described by Geevarghese[20] in south Indian patients was pain between the ages of 6-10 years, diabetes by the age of 20 years, and death before the age of 30. However, recent studies from South India have suggested that the profile of ICP is changing. In our cohort of ICP patients, 43% were above 30 years and better nourished (BMI: 20.5+3.2 kg/m^2). The classical TCP, where most of the patients were between 10 to 30 years, malnourished, and had a high frequency of diabetes, calcification, and risk of malignancy, is now seldom seen. In a multicentric study from India involving 1086 subjects with CP, only 3.8% fit into the classic TCP diagnosis. There has been a changing trend in the spectrum of CP in India over the years. TCP and ICP seem to be a complex disorder with the interaction between genes and the environment. Because the genetic profile of an individual cannot change, change in phenotypic presentation of TCP/ ICP over time could be due to the changes in the environment, diet, smoking habit, and nutritional status. Therefore, it can be safely assumed that patients who used to present earlier as TCP are now present more often as ICP due to the influence of environmental changes, and both TCP and ICP may be different phenotypic presentations of genetically predisposed similar individuals.

The association between CP and pancreatic cancer is considerably high. Lowenfels *et al*.[21] reported an estimated risk of malignancy around 4% at 20 years in a large multicentre study on chronic alcoholic pancreatitis. Multiple reports from India have found that that the risk of pancreatic cancer was higher in patients ICP as compared to those with alcoholic CP.

A study by Augustine P and Ramesh H have found pancreatic adenocarcinoma in 22 of 266 patients (8.3%) with TCP and suggested TCP may be a premalignant condition.[22-24] The prevalence of malignancy in our cohort

of ICP was high (13.5%), even in those with early-onset ICP. However, it cannot be taken as a true prevalence of malignancy in ICP patients, as hospital-based data is subject to referral bias. The exact incidence and prevalence of adenocarcinoma complicating CP in India may be known only after conducting large population-based prospective studies. One important feature observed in our series was a significant number of patients of ICP with head mass turning out to be malignant (17/43; 40%). Thus head mass in the background of ICP should raise high suspicion of malignancy.

There are two studies published from Eastern India by Bhattacharjee *et al*., and Jha *et al*.[25-26] have included CP patients of all aetiologies, and our study provides data exclusively on idiopathic CP. The mean age of ICP patients in our study was 31.5 years, comparable to the mean age in a study by Bhattacharjee *et al*. (29.7 years). The mean age in the study by Jha *et al*. was 39.5 years, in which 34% of patients had alcoholic CP (**Table 2**).

The prevalence of biliary stricture in our study (5.25%) is similar to (5.5%) to that in the study by Bhattacharjee *et al*. from Eastern India. However, in another study from Eastern India by Jha *et al*., the prevalence of biliary stricture was 19.4%, though only 6.4% of patients had a symptomatic biliary stricture. Therefore, a stringent assessment of bile duct by MRCP or ERCP could result in the detection of asymptomatic biliary stricture in a higher proportion of CP patients.

Surgical treatment was offered in a higher proportion (69.7%) of CP patients in our series. In a study by Bhattacharjee *et al*. from Eastern India, about 40% of patients required surgery. Ours is a resource constraint region where patients often cannot afford costly treatment, particularly the ones which require multiple sessions and regular/prolonged abstinence from the work. Moreover, accesses to the repeated endoscopic therapy or extracorporeal shockwave lithotripsy are limited in Bihar. Therefore, we have to keep the threshold for surgical therapy on the lower side, which results in a higher proportion of patients undergoing surgical therapy.

The morbidity and mortality of side to side LPJ is <1%. Our study found that one-time surgery has excellent long-term pain relief with minimal morbidity.

The limitations of our study are smaller sample size and potential biases arising due to local referral patterns.

In conclusion, our findings suggest that ICP is the most common cause of CP in Eastern India. It resembles TCP described in south India with a high incidence of diabetes and malignancy. There were no statistically significant differences in the rate of complications between early and late-onset ICP. Further population-

Table 2: Comparison of results of current study with those from different parts of India.

Study/Years	Region	N	Etiology	Mean Age	Male	Diabetes	Steatorrhea	Head Mass	Biliary Stricture	Calculi/ Calcification	Malignancy
Current 2018	Eastern	129	Idiopathic Only	31.5 yrs	55%	25%	6.2%	33%	5.2%	100%	13%
Jha AK *et al* 2017	Eastern	139	Mixed ICP: 50.3%	39.5 yrs	76%	45.3%	14.3%	2.8%	19.4%*	68.3%	0.7%
Bhattacharjee PK *et al* 2015	Eastern	145	Mixed ICP: 44-4%	29.7 yrs	79%	44.8%	EPI: 41.3%#	5.5%	5.5%	Calculi: 66% Calcification: 31%	00
Bhasin DK *et al* 2009	North	64	ICP	33.0 yrs	65.6%	23.4%	12%	NA	NA	46.8%	00
Balakrishnan *et al* 2006	South	244	TCP	30.5 yrs	70%	59.7%	Nil	NA	NA	90%	Very high

Abbreviations: ICP: Idiopathic chronic pancreatitis, EPI: Exocrine pancreatic insufficiency, NA: data not available

*Symptomatic: 6.4%

#EPI was defined as the presence of clinical steatorrhea and its improvement by pancreatic enzyme supplementation or fecal pancreatic elastase level <200 µg/g of stool.

based studies, including a study on a genetic basis, are needed to expand the results of our study.

References

1. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120: 682–707.
2. Tandon RK, Sato N, Garg PK. Chronic pancreatitis: Asia-Pacific consensus report. J Gastroenterol Hepatol. 2002;17:508–18.
3. Garg PK. Chronic pancreatitis in India and Asia. Curr Gastroenterol Rep. 2012;14:118–24.
4. Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia- Pacific region. J Gastroenterol Hepatol. 2004;19:998–1004.
5. Tandon RK, Garg PK. Tropical pancreatitis. Dig Dis. 2004;22:258–66.
6. Balaji LN, Tandon RK, Tandon BN, *et al*. Prevalence and clinical features of chronic pancreatitis in southern India. Int J Pancreatol 1994;15:29 –34.
7. Chari ST, Mohan V, Jayanthi V, *et al*. Comparative study of the clinical profiles of alcoholic chronic pancreatitis and tropical chronic pancreatitis in Tamil Nadu, South India. Pancreas 1992; 7:52–58.
8. Balakrishnan V, Sauniere JF, Hariharan M, *et al*. Diet, pancreatic function, and chronic pancreatitis in South India and France. Pancreas 1988;3:30–35.
9. Mori M, Hariharan M, Anandakumar M, *et al*. A case-control study on risk factors for pancreatic diseases in Kerala, India. Hepatogastroenterology 1999;46:25–30.
10. Thomas PG, Augustine P, Ramesh H, *et al*. Observations and surgical management of tropical pancreatitis in Kerala and south- ern India. World J Surg 1990;14:32–42.
11. Khan AA, Ali L. Tropical calcific pancreatitis and fibrocalculus pancreatic diabetes in Bangladesh. J Gastroenterol Hepatol 1997;12:S48 –S52.
12. Balakrishnan V, Unnikrishnan AG, Thomas V, *et al*. Chronic pancreatitis. A prospective nationwide study of 1,086 subjects from India.JOP. 2008;9:593–600.
13. Balakrishnan V, Nair P, Radhakrishnan L, Narayanan VA. Tropical pancreatitis—a distinct entity, or merely a type of chronic pancreatitis? Indian J Gastroenterol. 2006;25:74–81.
14. Bhasin DK, Rana SS, Chandail VS, Singh G, *et al*. Clinical profile of calcific and noncalcific chronic pancreatitis in North India. J Clin Gastroenterol. 2011;45:546–50.
15. Lankisch PG, *et al*. The course of pain is the same in alcohol and non alcohol induced chronic pancreatitis. Pancreas. 1995;10(4):338–41.
16. Shimosegawa T *et al*. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–358.
17. Layer P, Yamamoto H, Kalthoff L, *et al*. The different courses of early and late onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology 1994;107:1481–1487.
18. Garg PK, Tandon RK. Two different patterns of tropical pancreatitis: One disease or two? J. Gastroenterol. Hepatol. 2000; 15 (Suppl.): A205 (Abstract).
19. Rajesh G, Veena AV, Menon S, Balakrishnan V. Clinical profile of early-onset and late-onset idiopathic chronic pancreatitis in South India.Indian J Gastroenterol 2014;33.
20. GeeVarghese PJ, Pillai VK, Joseph MP, Pitchumoni CS. The diagnosis of pancreatogenous diabetes mellitus. J Assoc Physicians India 1962; 10:173-78.
21. Lowenfels AB, Maisonneuve P, Cavallini G *et al*. Pancreatitis and the risk of pancreatic cancer. International pancreatitis study group. N Engl J Med. 1993;328:1433-7.
22. Chari ST, Mohan V, Pitchumoni CS, *et al*. risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. Pancreas. 1994;9:62-6.
23. Augustine P, Ramesh H. Is tropical pancreatitis premalignant? Am J Gastroenterol. 1992;87:1005-8.
24. Mori M, Harihran M, Anandkumar M, *et al*. a case control study on risk factors for pancreatic disease in Kerala, India. Hepatogastroenterology. 1999;46:25-30.
25. Bhattacharjee PK *et al*. Demography and clinicopathological profile of patients with chronic pancreatitis in a tertiary referral teaching hospital of west Bengal:personal experience. Indian J Gastroenterol 2015; 34:365–371
26. Jha AK *et al*. Chronic pancreatitis in Eastern India: Experiance from a tertiary care center. Indian J Gastroenterol.2017;36:131-136.