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REVIEW ARTICLE

The Current Concepts and Management of Idiopathic (Tropical) Chronic Pancreatitis

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Abstract

Tropical chronic pancreatitis (TCP) is a special variant of idiopathic chronic pancreatitis that is seen mainly in tropical countries. Although the prevalence of tropical pancreatitis is high in southern India, it is reported from most parts of India. It occurs usually in young people, involves the main pancreatic duct, and results in large ductal calculi with high incidence of diabetes and malignancy. Recent reports suggest that the presentation is changing. The age of onset is older and the disease course seems to be milder. The etiology is not known, but genetic mutations and environmental factors are likely causes. This article is a narrative review of the recent trends in the etiopathogenesis and management of tropical calcific pancreatitis (TCP). Extensive literature search was done from PubMed and Ovid. Article was prepared by reviewing full-text articles and abstracts related to chronic calcific pancreatitis (CCP) and TCP.

Keywords Tropical pancreatitis · Idiopathic chronic pancreatitis · Chronic calcific pancreatitis

Introduction

Chronic calcific pancreatitis (CCP) is a condition characterized by progressive inflammation of pancreas that results in irreversible destruction and fibrosis of the pancreatic tissues leading to exocrine and endocrine dysfunctions [1]. While the predominant cause of CP in the Western world is alcoholism, in the developing world it is idiopathic CP (ICP) [2]. Tropical chronic pancreatitis (TCP) is a form of ICP seen almost exclusively in tropical and subtropical countries, characterized by abdominal pain, large pancreatic intraductal calculi, high probability of developing insulin-dependent but ketosis-resistant diabetes mellitus (DM), and increased risk of pancreatic carcinoma in young, non-alcoholic patients [3]. The current article provides an overview of clinical-epidemiological profiles, complications, treatment, and outcome of TCP/ICP.

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Epidemiology and Etiology

Whitcomb suggested that CP may be classified according to risk factors—toxic, idiopathic, genetic, autoimmune, obstructive, and recurrent acute—the TIGAR-0 classification [1]. Alcohol is the most common cause of CP worldwide, though its role as a distinct etiological factor is currently questioned. Smoking was earlier considered as a cofactor with alcohol in the pathogenesis of CP; recent population-based studies have demonstrated smoking as an independent risk factor [4]. Among the Asia-Pacific countries, alcohol is the etiology in 95% of CP in Australia, 70% in the Republic of Korea, and 54% in Japan. In India and China, on the other hand, over 70% patients with CP have idiopathic chronic pancreatitis (ICP) [2]. Oxidative stress and genetic mutations are the predominant factors that have emerged as the risk factors in patients with ICP in India. CP is endemic in South India with a prevalence of 126/100,000 population as shown in population-based studies in Kerala [5]. Even in Eastern India, ICP is the commonest variant of CP [6].

The classical TCP, where most of the patients were between 10 and 30 years, malnourished, and had high frequency of diabetes, calcification, and risk of malignancy, is now seldom seen. CP is also prevalent in other parts of India and the phenotype currently seen all over the country (including South India) does not always match the one described as TCP, with only 3.8–5.8% patients satisfying the criteria. TCP was initially found to occur more commonly among poor and malnourished population of developing countries. It is now believed that maldigestion due to CP may be one of the important reasons behind malnutrition.

The dietary toxins such as cassava (*Manihot esculenta*) containing varying amounts of cyanogen glycosides were implicated in the pathogenesis. This was based on the reports of an epidemiological association between consumption of cassava and prevalence of TCP in Kerala. The detoxification of cyanogen glycosides requires sulfur-containing amino acids which are deficient in malnourished individuals. However, TCP was found to be uncommon in several populations eating large amount of cassava and cases of TCP have been reported from several parts of India and the world where cassava is not consumed. A case control study has found a lack of association between consumption of cassava and occurrence of TCP [7].

TCP may affect members of the same family. Familial aggregation has been reported in TCP. In a study, familial aggregation was seen in 8% of TCP patients [8].

The patients who used to present earlier as TCP now present more often as ICP due to the changes in the environment, diet, smoking habit, and nutritional status.

Clinical Profiles

In general, the clinical picture of CP consists of a triad of pain abdomen, pancreatic calculus, and diabetes [9]. Patients with TCP in addition have characteristic features like emaciation, parotid enlargement, and a distended abdomen [10]. However, recent reports suggest that clinical presentation is changing which may be because of the improved nutritional status [11, 12]. TCP is usually seen in children and young adults; however, age of onset is now getting older [13–15]. Clinical profile of ICP patient in various Indian studies has been summarized in Table 1 [6, 16, 17, 19, 20].

Abdominal Pain

Abdominal pain is the predominant feature of TCP in up to 90% cases [21]. The pain is intermittent, severe, and located to the upper abdominal radiating to the back, and is relieved by leaning forward. The cause of abdominal pain in TCP may be due to disease process itself, and development of complication such as pseudocysts or pancreatic malignancy. The severity of the pain tends to diminish in parallel with the disease progression. A small proportion of patients with CP may run a painless course. Even though it appears that with gross parenchymal destruction the pain would decrease or even disappear, this appears unlikely and pain could progress even after pancreatic atrophy. Even after total pancreatectomy, analgesic is required in 40% of patients [22]. Recent evidence suggests importance of identification of neuropathic factor in pain, though there are currently no specific clinical tools to confirm neuropathic pain.

Pancreatic Calculi

Pancreatic calculi are very common in patients with TCP and may be detected in over 90% cases [23]. The locations of calculi are mainly intraductal in the region of head and uncinate process. The calculi may be solitary or multiple, and at times very extensive involving the entire pancreas. The calculi of TCP tend to be large and rounded which contrasts with the small and speckled calculi in patients with alcoholic CP [24].

Steatorrhea

Clinical manifestations of pancreatic enzyme insufficiency (PEI) appear when pancreatic exocrine secretion falls to below 10% of normal. It occurs after development of gross pancreatic atrophy or obstructing calculi in the head of pancreas. Steatorrhea, progressive weight loss, and deficiency of fat-soluble vitamin are important manifestations. Overt steatorrhea, consisting of passing bulky, frothy, or oily stools, is uncommon in patients with TCP. This may be due to consumption of low fat by affected individuals [25].

Diabetes

Diabetes in TCP is called fibrocalculous pancreatic diabetes (FCPD) [26]. Diabetes is a relatively late feature in the natural course of TCP. It often develops 10 years or more after first presentation as abdominal pain. It occurs in over 90% of patients and is more common than in patients with alcoholic CP. Diabetes in TCP is usually associated with marked hyperglycemia with requirement of insulin in the majority. One of the typical features of FCPD is that, despite insulin requirement, these patients rarely develop diabetic ketoacidosis. This may be due to the residual insulin secretion via partially preserved pancreatic beta cell, loss of glucagon reserve, and/or poor subcutaneous fat content causing inability to release the non-esterified fatty acids [27]. Though diabetes is a delayed manifestation of CP, clinical observations and experimental studies suggest that beta cell dysfunction and diabetes develop much earlier in India, occasionally with diabetes preceding the diagnosis of CP [28].

Table 1 Results of studies of ICP from different parts of India

Study/years	Region	Number	Etiology	Mean age	Male	Daibetes	Steatorrhea	Head mass	Biliary stricture	Calculi/ calcification	Malignancy
Anand et al. [6]	Eastern	129	Idiopathic only	31.5 years	55%	25%	6.2%	33%	5.2%	100%	13%
Palanivelu et al. (unpublished 2016)	Southern	64	TCP	39.21 ±9.39	44%	59%	22%	8%	NA	1	4%
Jha et al. [16]	Eastern	139	Mixed ICP: 50.3%	39.5 years	76%	45.3%	14.3%	2.8%	19.4%*	68.3%	0.7%
Bhattacharjee et al. [17]	Eastern	145	Mixed ICP: 44–4%	29.7 years	79%	44.8%	EPI: 41.3%#	5.5%	5.5%	Calculi: 66%; calcification: 31%	00
Bhasin et al. [18]	North	64	ICP	33.0 years	65.6%	23.4%	12%	NA	NA	46.8%	00
Balakrishnan et al. [19]	South	244	TCP	30.5 years	70%	59.7%	Nil	NA	NA	90%	Very high

Abbreviations: ICP, Idiopathic chronic pancreatitis; TCP, tropical 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

Pathogenesis

Abdominal Pain

An important pain mechanism that has emerged from recent clinical and experimental studies is oxidative stress and inflammation-induced pancreatic nociception and neuroimmune alteration [29]. Experimental evidence supports that intraductal and interstitial pancreatic pressure due to stricture or stone activates pancreatic stellate cells (PSC) which can generate oxidative stress and result in pro-inflammatory milieu within the pancreas.

Nociceptors are present in intra pancreatic sensory nerves and dorsal root ganglia. Mast cells, trypsin, or alcohol metabolites can bind to and activate these receptors. In addition, several neuroimmune alteration have been described in CP. Predominant among these includes infiltration of inflammatory cells (mast cells and eosinophils), neural edema, perineural disruption, and neural hypertrophy. Several factors namely glutamine calcitonin gene–related polypeptide (CGRP), substance P, and fractalkine (a neural cytokine) have been implicated in the causation of neural inflammation. The persistent inflammation and neuroplastic changes in the pancreatic nerves leading to continuous depolarization of these nerves result in the state of spinal hypersensitivity, a phenomenon known as global sensitization. These results in mechanical allodynia, i.e., generation of pain after physiological stimulus and inflammatory hyperalgesia, meaning amplified pain response to normal pain stimulus. Eventually, these events bring about a change in the entire cortical pain modulating neural network in the brain [30]. These events could explain persistence of pain even after total pancreatectomy.

Diabetes

Diabetes in CP has long been ascribed to pancreatic parenchymal fibrosis and loss of islet cells. Recent experimental studies have demonstrated that beta cell dysfunction even in the absence of beta cell death occurs due to inflammatory milieu provided by PSCs and T helper subsets infiltrating islet cells [31]. This may be the reason of improvement of the functional capacity of islet cell if inflammatory milieu within pancreas can be altered. One of the typical features of diabetes in CP is that, despite insulin requirement, these patients rarely develop diabetic ketoacidosis. This may be due to the residual insulin secretion via partially preserved pancreatic beta cell, loss of glucagon reserve, and or/poor subcutaneous fat content causing inability to release the non-esterified fatty acids [15].

Genetics of Chronic Pancreatitis

Cationic trypsinogen gene (PRSS1), pancreatic secretory trypsin inhibitor gene (SPINK 1), cystic fibrosis transmembrane conductance regulator gene (CFTR), chymotrypsinogen C (CTRC), cathepsin B (CTSB), calcium-sensing receptor (CaSR), and carboxypeptidase 1 (CPA 1) are the foremost genetic mutation and polymorphisms recognized in CP [32, 33]. These mutations and polymorphisms have different mechanisms and variable penetrance. Hereditary pancreatitis (HP) is an autosomal dominant condition which is due to mutation in PRSS1 gene; a gain of function mutation is the

most potent [32]. Mutations and polymorphisms in other genes function as risk factors and disease modifiers. Genetic testing might be considered when patients have a family history of idiopathic CP, RAP, or childhood pancreatitis, have relatives with known mutations associated with HP, are younger than 25 years old, or have RAP of uncertain etiology [32].

Fibrosis

Progressive fibrosis in CP is mediated by pancreatic stellate cells (PSC). PSCs remain in quiescent state and maintain the pancreatic extracellular matrix. After exposure to oxidative stress (cigarette smoking and alcohol metabolites), and after recurrent acinar injuries, the PSCs transform into an activated phenotype that secrete a wide variety of cytokines. The cytokine responsible for fibrosis is TGF beta which lay down excess amount of collagen I in extracellular matrix.

Natural History

Sentinel acute pancreatitis event (SAPE) hypothesis suggests CP develops as a result of recurrent pancreatic injury at the acinar (trypsinogen activation) or ductal (improper bicarbonate secretion) level. The clinical course of CP can be arbitrarily divided into early (first 5 years) phase characterized by recurrent acute pain with or without overt acute pancreatitis whereas development of morphological changes such as pancreatic calculi, ductal strictures, and pseudocyst marks intermediate (5–10 years) phase. Pancreatic exocrine insufficiency and diabetes manifest by the late phase, although these may develop early specially in ICP [34].

Pathology

The main pathological features of TCP are progressive pancreatic fibrosis resulting in atrophy of the gland together with formation of calculi and dilatation of the pancreatic ducts. Because the pathological changes progress over period of time, the findings would depend on the disease stage at which the tissue is obtained.

Gross Findings

The size of the pancreas decreases with the progression of the disease. The shape may be distorted, and surface is irregular with thickened capsule. The pancreas becomes hard and coarse. The cut section of the pancreas reveals the presence of fibrosis and intraductal and marked dilation of the main pancreatic ducts and its branches. Pancreatic calculi are made of calcium carbonate (>90%) with small amount of other calcium salts [35].

Microscopy

The hallmark is extensive generalized intralobular and interlobular fibrosis. Marked ductal dilatation with periductular fibrosis is noted involving main duct, collecting ducts, and small ductules with denudation of the ductular epithelium and squamous metaplasia in some areas. There is marked infiltration of the pancreas with lymphocytes and plasma cells, distributed mainly in periductal region [36]. Generally, there is a loss of pancreatic islets with some residual islets may show hyperplasia and beta cell proliferation.

Investigations

Diagnosis of CP requires demonstration of morphological and functional (exocrine and endocrine) alterations. The presence of pancreatic calculi is the key to the radiological diagnosis and occurs in over 90% of patients with TCP. A standard abdominal radiograph can detect the disease in about 35% of cases where extensive large calculi had already formed, but detection of early cases remains a challenge. Transabdominal ultrasound (USG) and contrast-enhanced computed tomography (CECT) scan of abdomen provide evidence of pancreatic atrophy, ductal dilatation, stricture, localization of pancreatic stones and calcification, and complications such as pseudocyst and presence of cancer. Magnetic resonance imaging with cholangiopancreatography (MRI/MRCP) is helpful in identifying altered ductal anatomy such as dilatation, strictures, leaks, and communication between the pancreatic duct and pseudocyst. The above tests are not very sensitive in detecting early changes of CP, in which case endoscopic ultrasound (EUS) plays an important role [37]. But EUS is operator-dependent and has the tendency to over diagnose early CP.

Pancreatic function tests (direct and indirect) can be used to assess secretory function of pancreas. The sensitivity and specificity to detect CP exceeds over 80% but the capability to diagnose early CP is not clear. The secretin MRCP test is another direct pancreatic functional test that has advantage of detecting functional as well as structural changes of pancreas simultaneously.

Complications

Patients of CP may develop pseudocysts, ascites, obstructive jaundice, and malignancy. Pancreatic cancer is the gravest complication of CP. The overall risk of developing pancreatic cancer among patients with CP has been estimated to be 16.5-fold higher than age-matched controls [38]. The clinical series suggest that the risk in patients with TCP is higher than in other forms of CP. The reason for the higher incidence of

cancer in TCP remains unknown. The presence of head mass in the background of chronic pancreatitis presents great diagnostic and therapeutic dilemmas and malignancy needs to be ruled out with certainty. While a positive biopsy is useful, a negative biopsy does not rule out malignancy. Presently, EUS FNA and CA 19-9 on the background of clinical conditions may provide important clue but with high false negative results.

Management

The aims of treatment in CP include pain relief, correction of exocrine and endocrine pancreatic insufficiencies, and nutritional support. Patient counselling is required regarding abstinence of alcohol and smoking.

Abdominal Pain

It is important to know the cause of pain as it may be due to chronic pancreatitis itself or may be due to complications like pseudocyst, duodenal/biliary obstruction, and pancreatic malignancy. Therefore, it is important to assess the disease morphology prior to initiation of treatment. Several options including medical, endoscopic, and surgical treatment are available for management of pain.

Analgesics

A graded approach is usually adopted while selecting therapeutic agent for pancreatic pain, beginning with nonsteroidal anti-inflammatory drugs. Low potency selective μ-opiate agonist such as tramadol hydrochloride has been found to be equally effective with better safety profile than high potency narcotics such as morphine. High potency narcotics such as morphine should be avoided [29].

Antioxidants

The primary aim of antioxidant therapy in CP is to supply methyl and thiol moieties for the intra-acinar transulfuration pathway which is essential in protecting against oxidative stress [39]. Two recently published meta-analysis have shown that antioxidant combination containing organic selenium, ascorbic acid, beta carotene, methionine, and alfa-tocopherol is effective in improving pain. All the components are required in higher dose and most important among them is methionine at a dose of 2–4g daily [40, 41].

Neural modulator pregabalin in higher dose from 150 to 600 mg per day demonstrated significant reduction in pain in patients with CP when treated for 3 weeks in a randomized control trial [42].

A recently randomized control trial demonstrated that a combination of methionine containing antioxidants and pregabalin resulted in significant reduction of pain in patients with CP who had recurrence of pain after ductal clearance with endotherapy or surgical drainage [43].

Pancreatic Enzyme Supplements for Pain

Pancreatic enzyme supplementation has been used in clinical practice for controlling pain in CP. This is based on the assumption that proteins in food bind to duodenal CCK receptors that result in pancreatic enzymes secretion which may cause ductal hypertension. The proteases in pancreatic enzymes bind to CCK receptors leading to suppression of pancreatic secretion and reduction in intraductal pressure. The evidence for the use of pancreatic enzyme in pain relief has revealed conflicting results with some trials showing benefit and others do not [44, 45]. Individual studies with non-enteric-coated enzyme preparations showed good pain relief due to binding of non-enteric preparations with CCK in better way [18].

Pancreatic Exocrine Insufficiency

The mainstay of treatment of exocrine insufficiency remains pancreatic enzyme replacement therapy (PERT) which entails supplementation of lipase, amylase, and proteases. Lipase should be administered in enteric-coated form to prevent proteolytic digestion. It should be loaded into pellets of 2mm or less in size (microsphere) so that it can be delivered into duodenum along with chyme. The minimal daily requirement of lipase is 60,000 units [46]. The approximate dose requirement can be calculated based on fat content of diet. Pancreatic enzyme should be taken along with meal for proper mixing-up. It is advisable to prescribe proton pump inhibitor to provide extra resistance to acid digestion in addition to enteric coating [47].

Diabetes

The principles of management of diabetes in TCP patients remain like those in other types of diabetes. However, because of malnutrition, a more liberal calorie and protein intake may be advised in patients with TCP. Majority of patients need insulin for glycemic control of diabetes and overall wellbeing.

Endoscopic Therapy

The major indications for endoscopic therapy are obstructing intraductal stones, severe ductal stricture, pseudocyst drainage, and celiac plexus block. Large stones or impacted stones which are common in TCP usually require extracorporeal shockwave lithotripsy (ESWL) or intraductal lithotripsy; these

techniques apply shockwaves to break up stones. Two recent randomized controlled trials comparing surgical treatment over endotherapy have demonstrated the superiority of surgical therapy in pain relief and quality of life in patients with proximal duct obstruction [48, 49]. In a large multicenter study involving 1018 patients, the success of multiple sessions of endoscopic therapy was in 65% of patients and surgery required in 24% of patients [50]. In another study in 61 patients with CP and bile duct stenosis, the reported 1-year success rate with endoscopic stenting and stent replacement every 3 months was 59%, but there was a failure of endotherapy in patients with presence of calcifications where success rate was only 7.7% [51]. In patients with symptomatic pseudocysts without ductal obstruction, endoscopic drainage procedures may be considered as safe, effective treatment with success rates similar to that of surgical drainage [52].

Surgical Treatment of Chronic Pancreatitis

The indication of surgery in TCP is an intractable pain, significant local complications, unsuccessful endoscopic management, and suspicion of malignancy. Contrary to this step-up approach, early surgical intervention has gained momentum with the landmark publications from Nealon et al. [53] after two decades of the introduction of the Puestow procedure. Studies from other centers also supported the possibility of functional preservation of the gland with early surgery especially by drainage procedures [54]. Intervening after the onset of perpetual pain sensitivity in the central nervous system and narcotic addiction is associated with poor outcomes after surgery [55]. Surgery before increased sensitivity to pain may yield better results. With the publication of experimental and prospective analytical studies, Dutch pancreatitis group started a randomized controlled trial comparing early surgery and step-up approach [56].

The main goal of surgery is to control abdominal pain which is largely achieved in most series as noticed in the increase of BMI at follow-up after surgery, which is an indirect sign of improved quality of life. Surgery does not prevent deterioration of glandular function in the form of reversal of endocrine and exocrine insufficiencies after surgery [57]. Surgical procedures in CP can be divided into drainage operations and resections.

Pure Drainage Procedures

In patients with a ductal dilation without inflammatory mass in the pancreatic head, a lateral pancreaticojejunostomy (Partington-Rochelle procedure) represents an effective drainage operation [58, 59]. The primary success rate of this procedure is good, but their long-term outcome is poor. The results of procedures are good if the duct is substantially dilated (>7 mm) which is common in TCP.

Resections

There are a minority of patients with TCP present with a ductal obstruction located in the pancreatic head, associated with an inflammatory mass. In these patients, pancreatic head resection is the procedure of choice. The partial pancreatoduodenectomy (Kausch-Whipple procedure), in its classical or pylorus-preserving variant, has been the procedure of choice for pancreatic head resection in CP for many years. The duodenum-preserving pancreatic head resections and its modifications (Beger procedure, Frey-procedure, and Bern procedure) represent less invasive, organ-sparing techniques with equal long-term results [60–62].

In patients without mass in the pancreatic head and small duct disease (diameter of the pancreatic duct <3 mm), a V-shaped excision of the anterior aspect of the pancreas is a safe approach with effective pain management [63].

Laparoscopic Approach

Initial attempts to use laparoscopy in the management of chronic pancreatitis are reported, almost three decades ago, but apart from a small number of cohorts from selected centers, the progress has remained static [64, 65].

Technical Difficulties

Technical difficulties in laparoscopic pancreatic surgery are identifying the main pancreatic duct itself if not sufficiently dilated, lack of a marker to assess the depth of parenchymal resection, inability to clear the impacted calculi, and at times inability to identify the gastroduodenal artery.

Regarding the head coring in laparoscopic Frey's procedure, lack of posterior limit of head coring is the main limitation due to inability to palpate the posterior capsule and is considered a drawback in the laparoscopic approach of Frey's procedure. The amount of head coring to achieve optimal pain relief had been debated. Frey himself modified his technique and advised to limit the extent of head coring to the posterior surface of the pancreatic duct [66]. Moreover, conserving parenchyma may add to the preservation of gland function in surgical procedures for tropical pancreatitis in which exocrine and endocrine function of the pancreatic gland are affected earlier compared to the alcoholic counterpart in the Western world.

Conclusions

A large proportion of patients with CP have no identifiable cause which has been termed as idiopathic chronic pancreatitis (ICP). Though still controversial, ICP includes a number of well-described disease subgroups like early- and late-onset

ICP, tropical CP (TCP), minimal change CP, and small duct CP. ICP is the most common cause of chronic pancreatitis in India. The majority of such patients are young with slight male preponderance. They have significant risk of developing diabetes and pancreatic malignancy. They are poorly responsive to medical therapy, and the outcome of surgical therapy is good.

Author Contribution All authors contributed equally in searching the literature and drafting the manuscript.

Declarations

Conflict of Interest The authors declare no conflict of interest.

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