Clinicopathological Study of the Biliary and Duodenal Complications in Patients of Chronic Pancreatitis - A Prospective Observational Study in a Tertiary Care Centre in Eastern India

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ABSTRACT

BACKGROUND

Chronic pancreatitis is a chronic inflammatory disease, causing complications related to the duodenum like duodenal obstruction or complications related to the biliary system like cholestasis, cholangitis, secondary biliary cirrhosis and cholangiocarcinoma. The purpose of the study was to observe the occurrence, clinical manifestations and outcome of the complications and foster a deeper understanding of the long-term prognosis of patients suffering from chronic pancreatitis.

METHODS

This was a prospective observational study. After taking informed consent, total 50 patients admitted in hospital with features suggestive of chronic pancreatitis with or without duodenal or biliary complications were selected and were followed up throughout the course of the disease. All demographic parameters, diabetic status, liver function test, USG findings suggestive of duodenal obstruction or biliary abnormalities, upper GI endoscopy, computed tomography of whole abdomen, MR cholangio pancreatography and barium meal were studied.

RESULTS

Chronic pancreatitis is more common in male and the common age of presentation is between 45 and 54 years. 12 patients were diabetics. 42 % of the total 50 patients developed transient hyperbilirubinaemia. 5 male patients and 1 female patient had persistent hyperbilirubinaemia and had persistently raised values of alkaline phosphatase. 1 male and 2 female patients also suffered from hypoproteinaemia. About 42 % of the patients of chronic pancreatitis suffered from transient rise in conjugated bilirubin and were managed conservatively. 12 % of the patients suffered from persistently raised conjugated bilirubin, indicating biliary obstruction. 22 % of patients developed cholangitis responding to conservative management. 12 % of cases, 5 males and 1 female suffered from biliary stricture, and were managed surgically with hepaticojejunostomy. No cases of cholangiocarcinoma were detected.

CONCLUSIONS

The most common complication in patients of chronic pancreatitis is transient biliary stasis, others being cholangitis and persistent hyperbilirubinaemia. No cases of cholangiocarcinoma were detected.

KEYWORDS

Billiary, Duodenal, Complications, Stricture, Cholestasis, Cholangitis, Chronic, Pancreatitis

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BACKGROUND

The word "pancreas" is derived from the Greek name 'pan' (means: all) and 'kreas' (means: flesh). It is a retroperitoneal organ which lies obliquely, sloping upward from the C - loop of the duodenum to the splenic hilum. The study about this organ started since March 2, 1642, when a German émigré, Johann Georg Wirsüng, discovered the pancreatic duct in the San Francisco Monastery in Padua, Italy. Pancreatitis is inflammation of the gland parenchyma of the pancreas. In developed world, around 70 % to 80 % of patients suffering from pancreatitis have their manifestations in association with either biliary tract stone disease or ethyl alcohol abuse. Acute pancreatitis is mostly associated with biliary tract stone disease, whereas chronic pancreatitis is mostly associated with the ingestion of large amounts of ethyl alcohol over a prolonged period.

Chronic pancreatitis, by definition, is a progressive chronic inflammatory disease in which there is irreversible, progressive destruction of pancreatic tissue. Its clinical course is manifested by severe pain and in advance stages, both exocrine and endocrine pancreatic insufficiency. During evolution, in the early stages, it is mostly complicated by attacks of acute pancreatitis, which are responsible for the recurrent pain that may be the sole clinical symptom. It is generally believed that, in its earliest stages, chronic pancreatitis is an acute inflammatory process, and repeated episodes of subclinical acute pancreatic injury and necrosis lead to the fibrosis of pancreatic tissue which can exert extrinsic pressure on the pancreatic duct.[1] The intrapancreatic portion of the common bile duct, and the duodenal C-loop. With repeated attacks of pancreatitis, the glandular parenchyma is replaced by fibrous scar tissue, which can exert extrinsic pressure on the pancreatic duct, the intrapancreatic portion of the common bile duct, and the duodenal C-loop.

The end result can be complications related to the duodenum like duodenal obstruction or complications related to the biliary system like cholestasis, cholangitis, secondary biliary cirrhosis, and cholangiocarcinoma. These developments are variable, and individual patient with chronic pancreatitis may present with all, some, or none of these manifestations.

Among the patients who are admitted in hospital with pancreatitis, the incidence of biliary stricture is 6% and incidence of duodenal obstruction[2] is 1.2 %. But for patients requiring surgical intervention for chronic pancreatitis, the incidence of biliary stricture is found to be increased to 35 % and 12 % for duodenal obstruction. Obstruction of bile flow is due to stenosis that occurs due to fibrosis around the distal common bile duct (CBD).[3] The spectrum of patients may vary from being asymptomatic to being septic with cholangitis[4] along with increased levels of alkaline phosphatase or bilirubin, or both. Patients of pancreatitis with biliary stricture present more frequently with cholangitis, jaundice, hyperbilirubinemia, and persistent elevation of serum alkaline phosphatase.[5] Among these patients, 10% are diagnosed to be suffering from biliary cirrhosis and 10% suffering from cholangitis. Endoscopic retrograde cholangiopancreatography (ERCP) is the ideal investigation and it reveals a characteristically short, smoothly tapered stricture of the intrapancreatic common bile duct.

The actual factors for duodenal obstruction that convert self-limiting oedema to chronic fibrosis and stricture formation are unknown. The ischaemia of wall superimposed on inflammation is considered to be the major cause.[6] These patients suffers from a prolonged history of nausea and vomiting. Barium studies in these patients show a long segment of constricted duodenum, and endoscopy in these narrowed duodenum reveals reactive inflammatory changes.[7]

The end result can be complications related to the duodenum like duodenal obstruction or complications related to the biliary system like cholestasis, cholangitis, secondary biliary cirrhosis, and cholangiocarcinoma.[8] The study intends to throw a light on the incidence, clinical manifestations and outcome of the aforementioned complications and foster a deeper understanding of the long term prognosis of patients suffering from chronic pancreatitis.

Objectives

The objectives were to identify the various complications of the biliary system and duodenum associated with chronic pancreatitis and to explore or to observe the clinical manifestations, laboratory parameters and imaging modalities essential for early diagnosis of biliary and duodenal complications of chronic pancreatitis.

METHODS

Patients of chronic pancreatitis admitted in different wards in a Tertiary Medical College and Hospital over a period of two years from 2011 to 2013 were included in this prospective observational study. 50 patients suffering from chronic pancreatitis which are complicated by diseases of the biliary system and the duodenum are segregated on the basis of history (H/O recurrent episodes of chronic upper abdominal pain, recent onset of diabetes, chronic steatorrhoea, jaundice, vomiting) clinical assessment and laboratory workup. The patients were investigated with imaging studies (USG upper abdomen, MDCT upper abdomen, static and dynamic MR cholangiopancreatography). The patients suggestive of biliary complications were selected on the basis of history (jaundice, fever with chills and rigor, pruritus); clinical assessment (icterus, raised body temperature); laboratory workup (raised alkaline phosphatase, raised bilirubin, raised total WBC count) and imaging studies. Patients of duodenal complications were selected on the basis of history (nausea, vomiting and pain); clinical assessment (abdominal distention, dehydration) and imaging studies (USG upper abdomen, barium meal). Patients suspected of pancreatic malignancy were excluded from the prospective observational study.

The following parameters were studied so that biliary and duodenal complications may be identified in cases of

chronic pancreatitis. Age and sex of the patient, diabetic status, complete haemogram, blood levels of total and conjugated bilirubin, alkaline phosphatase, total protein and albumin, ultrasonography (USG) findings suggestive of duodenal obstruction or biliary abnormalities, upper GI endoscopy, barium meal, computed tomography of whole abdomen and MR cholangiopancreatography.

The patients admitted in different wards with features suggestive of chronic pancreatitis were selected on the basis of history, clinical examination and laboratory work up. Among these, patients suggestive of duodenal or biliary complications were selected on the basis of proper history, clinical examination, laboratory workup and radio imaging techniques. The patients were followed up throughout the course of the disease with the aid of clinical examination and laboratory reports. Plan for analysis of data was done accordingly.

Statistical Analysis

Data analysis was done by standard statistical method. We used statistical package for the social sciences (SPSS) software version 16 for this purpose. The continuous variables are number of patients, mean age and range. All categorical variables were reported as number (%) compared among different groups for independence of attributes.

RESULTS

Total 50 patients were included in our study. Among them 37 were male patients and 13 were female patients. Chronic pancreatitis was found to be majorly present in males with M : F – 2.85 : 1

Age Group in Years	Male	Female	Total
15 - 24	1	0	1
25 - 34	1	1	2
35 - 44	8	5	13
45 - 54	21	5	26
55 - 64	4	0	4
65 - 74	2	2	4

Table 1. Age Distribution of Cases of Chronic Pancreatitis

	Transient Hyper Bilirubinaemia	Persistent Hyper Bilirubinaemia	Tansient Raised Alkaline Phosphatase	Persistent Raised Alkaline Phosphatase	Hypo Proteinaemia
Male	16	5	18	5	1
Female	5	1	5	1	2
Total	**21 (42 %)**	**6 (12 %)**	**23 (46 %)**	**6 (12 %)**	**3 (6 %)**

Table 2. Distribution of LFT Parameters in Chronic Pancreatitis

The most common age of presentation is between 45 to 54 years in both males and females. The lowest age of presentation is 15 years. The highest age of presentation is 72 years. Mean age of presentation is 46.96 years. In every age group, males almost invariably out represent females. Among 50 patients, 12 patients (24 %) were diabetics. 2 of the males and 1 female were known diabetic, others had new onset diabetes.

42 % of the total 50 patients developed transient hyperbilirubinaemia. 5 male patients (13.5 %) and 1 female patient (7.7 %) had persistent hyperbilirubinaemia and also persistently raised values of alkaline phosphatase. 1 male (2.7 %) and 2 female (15.4 %) patients also suffered from hyoproteinaemia.

About 42 % of the patients of chronic pancreatitis suffered from transient rise in conjugated bilirubin, but the levels came down once the oedema subsided. 12 % of the patients suffered from persistently raised conjugated bilirubin, probably indicating some form of biliary obstruction.

	Cholestasis (Transient)	Cholangitis	Biliary Stricture	Cholangio Carcinoma	Operated
Male	16 (43.24 %)	8 (21.62 %)	5 (13.51 %)	0 (0 %)	5
Female	5 (38.46 %)	3 (23.08 %)	1 (7.69 %)	0 (0 %)	1
Total	**21 (42 %)**	**11 (22 %)**	**6 (12 %)**	**0 (0 %)**	**6 (12 %)**

Table 3. Biliary Complications in Chronic Pancreatitis

About 42 % of the cases suffered from transient cholestasis and they were managed conservatively. 22 % of patients developed cholangitis, which responded to conservative management. 12 % of cases, 5 males and 1 female suffered from biliary stricture, managed surgically with hepaticojejunostomy. No cases of cholangiocarcinoma as a complication of chronic pancreatitis was detected in this short period of time.

Sex	Duodenal Obstruction	Operated
Male	2	1
Female	0	0
Total	**2 (4 %)**	**1 (2 %)**

Table 4. Duodenal Obstruction in Chronic Pancreatitis

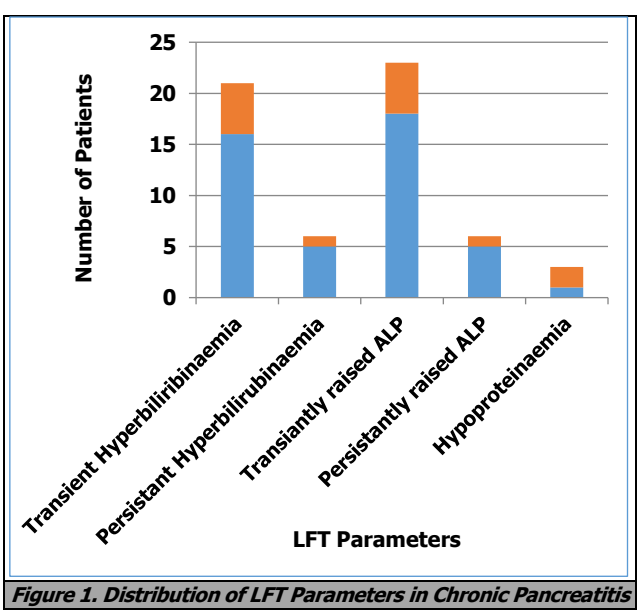

Figure 1. Distribution of LFT Parameters in Chronic Pancreatitis

DISCUSSION

The patients who suffer for a long time from chronic pancreatitis have sometimes found to develop complications related to the biliary system or the duodenum. This is due

to the close anatomical relationship of the distal common bile duct and the duodenum with the head of the pancreas.

Among the different complications of chronic pancreatitis, common bile duct stenosis is a well-recognized complication but its incidence, significance and natural history is uncertain.[9] The study was conducted to observe the occurrence, clinical manifestations and outcome of the complications. Different literature has described incidence of common bile duct stenosis which varies widely and is difficult to evaluate because the selection criteria for patients and the diagnostic test varies in these different studies.[10] Radiological evidence of common bile duct stenosis was found by Sarles et al. in 63 % of a series of 100 patients with chronic calcifying pancreatitis.[11] Aranha GV et al. conducted a study and lowest incidence of common bile duct stenosis (4 %) was reported from a large series of 1262 patients.[12] No biochemical or radiological investigation were done for screening these patients for the presence of common bile duct stenosis. It only represents the small proportion of patients who were clinically diagnosed as bile duct obstruction. it undoubtedly underestimates the true incidence of common bile duct stenosis. Bile duct abnormalities were associated more commonly with severe chronic pancreatitis, as assessed by ERCP, than in mild cases (69 % v 28 %) and this may also account for the different incidence reported in various series.

In a study by Sarles J.C., Nacchiero M., Leandri R. et al.[13] amongst 146 patients operated on for chronic calcifying pancreatitis, 135 were men and 11 were women whereas Jean-Marc Regimbeau, David Fuks et al.[14] found that among 39 patients 35 were men and 4 women. In the present study, of the total 50 patients suffering from chronic pancreatitis 37 (74 %) were male and 13 (26 %) were female. This is consistent with our knowledge of chronic pancreatitis that is found more in males than females. The ratio between males and females was 2.85 : 1.

The mean age of presentation was 46.96 years and the most common age group affected was between 45 to 54 years. The highest number of males (21) and females (5) were found in this age group only. It is to be noted that in every age group, the males invariably out represent the females. The highest age of presentation was 72 years but the disease commonly affects the middle aged. Interestingly enough, one male presented with chronic pancreatitis at the young age of 15 years.

Of the total 50 patients, 12 (24 %) were diagnosed as diabetic. 9 of them were male and 3 were female. Seven of the males and two females were diagnosed as new onset diabetes. Of the 1,086 patients studied by Balakrishnan et al. four hundred and eighteen (40.5 %) subjects had diabetes mellitus.[15] The high incidence of diabetes in patients of chronic pancreatitis indicate the fact that chronic pancreatitis leads to destruction of gland parenchyma and hence leads to endocrine insufficiency.

According to Rhormann et al. the most common complication of chronic pancreatitis is biliary obstruction which can occur in upto two thirds of cases. In most cases jaundice is either transient and of short duration due to pericholedochal oedema.[16] In a study by Jose Eduardo Monteiro da Cunha et al.[17] Out of a series of 149 patients operated for chronic pancreatitis, 45 (30.2 %) with common duct stricture secondary to pancreatic disease have been studied. 11 patients (24.4 %) had transient jaundice, 11 (24.4 %) persistent cholestasis and 6 (13.3 %) presented cholestasis with cholangitis. Seventeen patients (37.7 %) were considered to have asymptomatic biliary tract stenosis. In the present study, out of the total 50 patients, 21 (42 %) had transient rise of conjugated bilirubin in their blood. Of them, 16 were males and 5 were female. Transient rise of alkaline phosphatase in blood was seen in total 23 (46 %) patients. This rise in conjugated bilirubin and alkaline phosphatase was transient due to the presence of pericholedochal oedema, and once the oedema subsided, the jaundice also subsided. But among the 50 patients, 5 male and 1 female making a total of 12 % of the subjects developed persistent conjugated hyperbilirubinaemia along with persistent rise in alkaline phosphatase levels. These were the patients which were later proven to have developed biliary stricture as a sequele of chronic pancreatitis. Similar type of results were attained by William K J Huizinga et al.[18] In a study of 509 patients presented with chronic pancreatitis, the incidence of clinically manifested fixed common bile duct (CBD) stenosis was 9 % (45 patients, 1 male and 2 females also had hypoalbuminaemia in the present study).

Transient cholestasis was the most common complication encountered in patients of chronic pancreatitis, manifesting in 43.24 % of males and 38.46 % of females. Cholangitis was found in 11 cases (22 %). 8 of them were male and 3 were female. 12 % of the study population, including 5 males and 1 female developed biliary stricture as a complication of chronic pancreatitis. According to Rhormann et al.[15] the prevalence of CBD stenosis in pancreatitis patients has varied from 3 to 46 % and cholangitis was found in only 9 % cases. In the current study all the 6 cases of biliary stricture were managed surgically by hepaticojejunostomy.

There were no complications in the post-operative period and no hyperbilirubinaemia was noted in the follow up period. Surgery was performed in patients with common bile duct strictures due to chronic pancreatitis where there was evidence of cholangitis, biliary cirrhosis, common bile duct stones, progressive strictures, elevation of alkaline phophatase and/or bilirubin for over a month, and an inability to rule out malignancy. The surgery of choice was a bilio-enteric bypass either choledochoduodenostomy or choledochojejunostomy. A cholecystoenterostomy is not a favoured option because of its higher failure rate (23%). Endoscopic stenting, though not recommended as a definitive therapy plays a major role in patients who are unfit for surgery.

Persistent duodenal obstruction, not responding with 1–2 weeks of conservative therapy, is an indication for bypass. The surgery of choice is a gastrojejunostomy. It is not uncommon to see that combined obstruction of the pancreatic duct, common bile duct, and duodenum will develop. Combined drainage procedures or resection are used to manage these problems.[13]

A study by Pramod K Garg in AIIMS, New Delhi showed that the prevalence of cholangiocarcinoma was 2.2 % of

patients with chronic pancreatitis.[19] But in our current study there was no evidence of cholangiocarcinoma developing as a complication of chronic pancreatitis. This is mainly due to the fact that the study included only 50 patients which is a small number for coming to a proper conclusion and also the study period being short as because cholangiocarcinoma is a very long-term complication of chronic pancreatitis.

In a three-year study of 878 patients with pancreatitis by Edward L. Bradley III, M.D., J. Luther Clements Jr, nine cases of duodenal obstruction associated with pancreatitis have been found.[20]

In the current study out of 50 subjects, 2 males presented with features of duodenal obstruction. One of them was due to a large pancreatic pseudocyst compressing upon the duodenum and was managed surgically by cystogastrostomy. The other was transient in nature due to periduodenal oedema and subsided once the oedema subsided.

The present study was only a humble effort to better understand the incidence and significance of the biliary and duodenal complications in patients of chronic pancreatitis and throws into sharp relief the fact that a larger study with adequate number of subjects and over a longer period of time is required to arrive at a better understanding of the sequele of chronic pancreatitis.

CONCLUSIONS

Chronic pancreatitis affects males more than females. The most common complication in patients of chronic pancreatitis is transient biliary stasis probably due to oedema occurring in about 42 % cases. Cholangitis is also a common complication found in 22 % of the cases. Persistent hyperbilirubinaemia due to biliary stricture was found in 12 % cases, managed by hepaticojejunostomy. No cases of cholangiocarcinoma were detected within this short period of time. Duodenal obstruction was found in 2 (4 %) cases. We see that biliary and duodenal complications in chronic pancreatitis though not common are still subjects under intense scrutiny and scientific study. The presentation, diagnosis and management of these cases are of paramount importance to us clinicians. The current study throws some light on the sequele of chronic pancreatitis but for results reflecting the true incidence of biliary and duodenal complications, a larger study with adequately large sample size and over a longer period of time is required.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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