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ORIGINAL ARTICLE

Progression of recurrent acute and chronic pancreatitis: A short-term follow up study from a southern Indian centre

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Abstract
Background Little data exist on the progression of recurrent acute (RAP) and chronic pancreatitis (CP) from regions from where the entity of tropical chronic pancreatitis was originally described. The study aimed to follow up patients with RAP and CP seen at a southern Indian centre for progression of disease over time.
Methods Prospectively enrolled patients with RAP and CP were followed up, and the alcoholic and idiopathic subgroups were assessed for progression of structural and functional changes in the organ.
Results One hundred and forty patients (RAP = 44; 31.4 %, CP = 96; 68.5 %) were followed up over a median 12.2 (interquartile range 12.0–16.8) months. The cause was alcohol in 31 (22.1 %) and not evident in 109 (77.8 %). The disease progressed from RAP to CP in 7 (15.9 %), 6 (16.2 %) out of 37 in the idiopathic and 1 (14.2 %; $p = 1.00$) out of 7 in the alcoholic subgroups. Three (42.8 %) and 1 (14.2 %) developed steatorrhea and diabetes mellitus (DM), respectively, and 2 (4.5 %) developed calcification. Established CP progressed in 19 (19.7 %), 1 (1.0 %), 5 (5.2 %), 2 (2.0 %) and 11 (11.4 %) newly developed DM, steatorrhea, calcification and duct dilation during follow up. Among the idiopathic and alcoholic CP, disease progression was seen in 15 (20.8 %) out of 72 and 4 (16.6 %) out of 24 respectively.
Conclusions Idiopathic RAP and CP progressed during the short-term follow up. This is similar to other etiological forms of pancreatitis, as described from elsewhere in the world.

Keywords Chronic pancreatitis · Longitudinal studies · Recurrent acute pancreatitis · Steatorrhea · Tropical pancreatitis

Introduction

Different etiological factors lead to chronic pancreatitis (CP); many of which are shared by acute pancreatitis (AP) also [1, 2]. Thus, it is not difficult to see why CP can potentially evolve from AP. Continuing insult to the pancreas in the form of repeated attacks of inflammation as seen in recurrent acute pancreatitis (RAP) understandably leads to CP in some, but not all patients [3, 4]. Even after the development of early morphological changes of CP, further damage to the organ can occur over time as evidenced by the development of large pancreatic calculi, ductal dilatation and exocrine and endocrine deficiency [5, 6]. The reasons for such progression are not fully understood. Continued tobacco smoking and alcohol intake are known to contribute [7, 8]. Understanding the progression of pancreatitis is important since it helps to predict the long-term outcomes and also to develop treatment strategies that may attenuate such progression [5].

A form of chronic pancreatitis referred to as tropical chronic pancreatitis (TCP) with onset of pain in childhood, diabetes at puberty and curtailed life expectancy has been described from southern India and elsewhere in the world, especially the tropics, and has been considered as a distinct entity [9–11]. Over the recent decades, the etiology and

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presentation of CP in India have been changing, and some authors have questioned the appropriateness of considering TCP as a definite disease entity [12–15]. The time from the onset of pain to the diagnosis of early onset-idiopathic CP (ICP) and late-onset ICP have been recently reported from India to be nearly 14 and 5 years, respectively [14]. Very little data exist on the early natural history of ICP or TCP or on its progression. The aim of our study was to follow up patients with RAP and CP seen at our centre in southern India for the progression of disease over time.

Methods

Patients

Patients with RAP and CP presenting to the Department of Gastroenterology and Hepatology, Kasturba Hospital, Manipal between June 2009 and June 2013 were prospectively enrolled. They underwent detailed evaluation for etiology and the presence of steatorrhea and diabetes mellitus (DM). The intensity of pain was assessed using a visual analogue scale (VAS) and the number of episodes and the duration of each episode were noted [16]. Alcohol was considered the cause when patients consumed more than 50 g per day [17]. Patients presenting with more than one episode of acute pancreatitis with complete resolution of symptoms in between and no evidence of CP on imaging were considered to have RAP [7, 18]. AP was defined according to the Atlanta criteria [19].

All recruited patients underwent abdominal ultrasonography (USG). Those without definite evidence of CP (any two of atrophy, duct dilatation and/or calcification) underwent one or more of the following to confirm the presence or absence of CP–endoscopic ultrasound (EUS), computed tomography (CT) scan, or magnetic resonance cholangiopancreatography (MRCP). Findings on endoscopic retrograde cholangiopancreatography (ERCP) were included if available. This approach is in keeping with recent guidelines on imaging in CP [20–22]. EUS was performed at least 4 weeks after an episode of pain and those with the findings "consistent with" or "suggestive of" CP as per the Rosemont criteria on were diagnosed to have CP. Those with normal or indeterminate findings were classified as having RAP [23]. CP was diagnosed on ERCP according to the Cambridge classification and the presence of pancreatic calculi and/or ductal changes on the other imaging modalities [20].

Patients with RAP who had treatable causes such as biliary calculi and microcalculi, hypercalcemia and hypertriglyceridemia were included only if another episode of pancreatitis occurred once the cause had been tackled. Those with obstructive pancreatitis due to neoplasia or superadded pancreatic cancer were excluded.

Treatment

Moderate to severe pain initially was managed with nil per oral and analgesics. Once the pain subsided, patients were managed with oral pancreatic enzyme supplements, a proton pump inhibitor and anti-oxidants. De-addiction therapy for alcohol dependence and abstinence from tobacco smoking were advised as appropriate. Those with no response to drug therapy underwent pancreatic papillotomy and stent placement as previously described [24], failing which, surgery was advised.

Follow up

Patients were prospectively followed up at least once every 3 months or more often if clinically indicated. Plasma glucose and glycated hemoglobin (HbA1c) were estimated at least once every 6 months; DM was diagnosed as per the American Diabetes Association criteria [25]. Random spot stool samples were collected every 6 months without any prior dietary alterations, and the results of fat excretion estimated by the acid steatocrit method on the first and the last samples during the study period were included for analysis [26]. Steatorrhea was defined as excretion of >7 g of fat per day. No time interval from the episode of pain was followed for obtaining the stool sample. One or more of USG, CT, EUS, MRCP or ERCP (as a part of therapy) were used image the pancreas as per clinical necessity, but at least once in 6 months. Progression of RAP to CP was diagnosed based on abdominal USG if the findings were unequivocal; otherwise, an additional imaging was done before CP was ruled out. CP was considered to have progressed if new onset calcification, ductal dilatation, steatorrhea or DM was detected.

Statistics

The SPSS version 15 (SPSS South Asia, Bangalore) was used. Continuous variables were expressed as mean (standard deviation [SD]) or as median (interquartile range [IQR]). Mann-Whitney test and chi-square test were used as appropriate. Repeated measures ANOVA was used to compare parameters at baseline and on follow up. If the data was skewed, two-way Friedman's test was used for analysis by 'R'. Kaplan-Meier estimates were used to determine the time to progression of disease in RAP and CP. A p-value of <0.05 was considered as statistically significant. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all patients.

Results

Of the 158 patients enrolled, 18 (11.3 %) were lost to follow up. Data from 140 patients (RAP = 44 (31.4 %); CP = 96 (68.5 %) were analyzed. The median (IQR) age at entry was 28.5 (19.0–40.0) years (Table 1). Patients with CP were significantly older ($p = 0.002$) and their duration of symptoms longer compared to RAP patients ($p = 0.02$). Seventy-four (77.0 %) patients with CP showed pancreatic calcification on imaging.

Follow up

Both the idiopathic and alcoholic groups were followed up under the same protocol. The durations of follow up were 12.2 (12.0, 16.5) and 12.0 (11.1, 16.0; $p = 0.210$) months in idiopathic and alcoholic RAP groups, respectively, and 12.1 (12.0, 15.8) and 13.1 (12.0, 17.2; $p = 0.414$) months in the idiopathic and alcoholic CP groups, respectively. Over a median follow up of 12.2 (IQR 12.0–16.8) months, 6 (54.5 %) of the 11 with RAP and 18 (90.0 %) of the 20 with CP who were tobacco smokers at entry continued smoking. One (14.2 %) of the 7 patients with alcoholic RAP and 12 (50.0 %) of the 24 patients with alcoholic CP continued to consume alcohol. No patient newly initiated alcohol consumption or tobacco smoking. Pancreatic papillotomy and stent placement were done in 29 (30.2 %) with CP; 3 (3.1 %) patients underwent surgery (Frey's procedure = 2, lateral pancreaticojejunostomy = 1). The median (IQR) VAS decreased significantly from 6.0 (4.0, 8.5) to 3.0 (0.0, 5.6; $p < 0.001$) in RAP and from 5.7 (4.0, 8.0) to 2.8 (0.0, 5.0; $p < 0.001$) in CP during follow up.

Progression of RAP to CP

Seven (15.9 %) of the 44 RAP patients progressed to CP, as evidenced by changes seen on EUS. In the idiopathic and alcoholic subgroups of RAP, the disease progressed in 6 (16.2 %) out of 37 and 1 (14.2 %) out of 7, respectively ($p = 1.00$). The median time for progression of RAP to CP was 20.0 (95 % CI, 11.6, 28.6; $p < 0.001$) months using Kaplan-Meier estimates (Fig. 1). All 7 patients with RAP at recruitment who subsequently progressed to CP on follow up had undergone EUS in addition to USG to exclude CP at baseline evaluation, 3 and 4 of them showing no evidence of CP or indeterminate for CP, respectively. CP was diagnosed during follow up in all 7 based on EUS findings 'consistent with CP'; two of these had shadowing calculi.

Progression of chronic pancreatitis

Chronic pancreatitis progressed further in 19 (19.7 %) patients, being equally common in the idiopathic and alcoholic subgroups (15 [20.8 %] vs. 04 [16.6 %]; $p = 0.774$). The median time for progression was 27.1 (95 % CI 21.5, 32.6; $p < 0.001$) months (Fig. 2). The progression was confirmed by new onset steatorrhea in 7 (07.2 %), DM in 1 (01.0 %), pancreatic calcification in 2 (2.0 %) and ductal dilation in 11 (11.4 %) patients, some patients having more than one of these changes.

Pain, calcification, steatorrhea and diabetes mellitus during follow up in RAP

Stool fat excretion, fasting blood sugar (FBS) and VAS for pain at baseline were similar in patients with RAP who did not progress to CP during follow up compared to those who did

Table 1 Baseline characteristics of patients with recurrent acute and chronic pancreatitis

Variables	RAP ($n = 44$)	CP ($n = 96$)
Age in years (median [IQR])	22.0 (18.0, 33.5)	31.0 (22.0, 43.7)*
Male/female	36:08	77:19
Alcoholic pancreatitis (%)	07 (15.9 %)	24 (25 %)
Idiopathic pancreatitis (%)	37 (84.0 %)	72 (75 %)
VAS (median [IQR])	6.0 (4.0, 8.5)	5.7 (4.0, 8.0)
Duration of symptoms (median [IQR]) in months	7.0 (4.0, 24.0)	24.0 (5.2, 48.0)*
Diabetes mellitus (%)	04 (09.0 %)	22 (22.9 %)**
Steatorrhea (%)	02 (04.5 %)	43 (44.7 %)**
Smokers (%)	11 (25.0 %)	20 (20.8 %)

Significance level at $p < 0.05$

RAP recurrent acute, *CP* chronic pancreatitis, *IQR* interquartile range, *VAS* visual analogue scale

*$p = 0.002$ for comparison of age (in years) and $p = 0.02$ for duration of symptoms in months by Mann-Whitney test; **$p = 0.05$ for DM; **$p < 0.001$ for steatorrhea by chi-square test

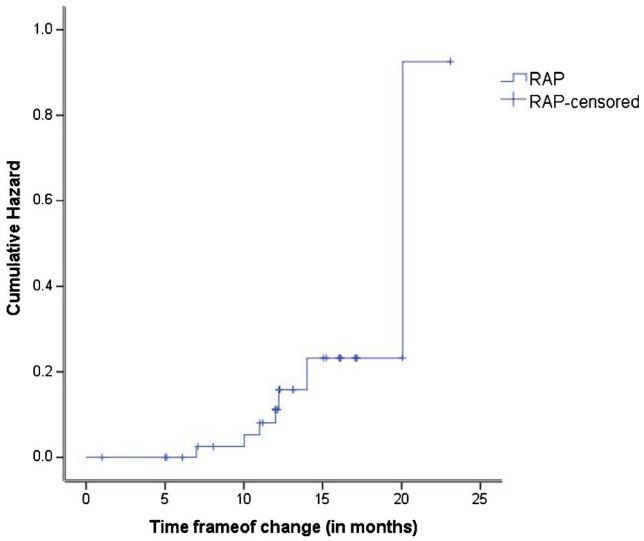

Fig. 1 Kaplan-Meier curves showing progression of recurrent acute pancreatitis to chronic pancreatitis

(Table 2). However, the VAS for pain at the end of follow up was significantly lower in the former patients compared to the latter.

Steatorrhea present in two patients with RAP at baseline returned to normal fat excretion at follow up; these patients did not progress to CP during follow up. Thus, exocrine insufficiency was present in none of the 37 who continued to have RAP at follow up. Among the 7 patients who progressed from RAP at baseline to CP, 3 (6.8 %) developed exocrine insufficiency at follow up. No patient with RAP developed new onset DM during follow up; none of the four diabetics with RAP developed features of CP. One (2.2 %) of these had a family history of DM, but not of pancreatitis. Two (4.5 %) patients with RAP had newly developed calcification during the follow up.

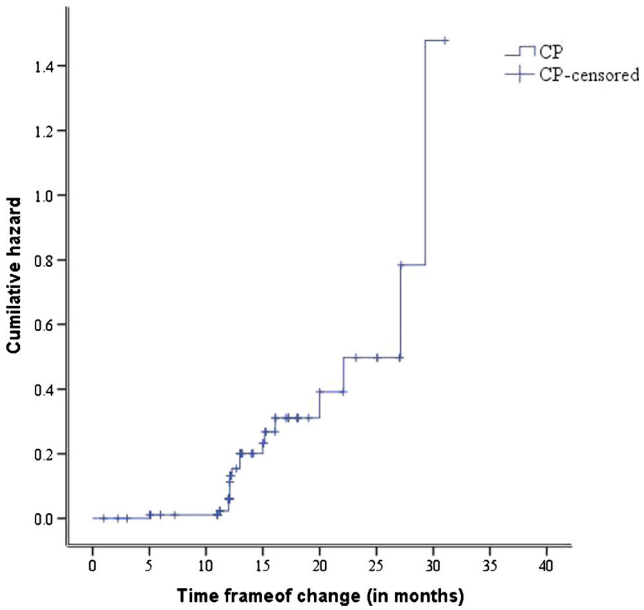

Fig. 2 Kaplan-Meier curves showing further progression in patients with chronic pancreatitis

Pain, calcification, steatorrhea and diabetes mellitus during follow up in CP

One (1.0 %), 5 (5.2 %), 2 (2.0 %) and 11 (11.4 %) of the 96 patients with CP at baseline newly developed DM, steatorrhea, calcification and duct dilation during follow up. Stool fat excretion, FBS and VAS for pain at baseline were similar in patients with CP who did not progress further during follow up compared to those who subsequently did (Table 3). However, the VAS for pain and the stool fat excretion were significantly lower in the former patients compared to the latter at the end of follow up.

Discussion

By following up patients with idiopathic and alcoholic RAP from a southern Indian centre, we have shown that these conditions progressed to CP in a proportion of patients. Similarly, CP also progressed over time as evidenced by new onset steatorrhea, the development of DM, calcification and ductal dilation. To the best of our knowledge, this is the first such study on patients from southern India or other tropical regions from where the entity of TCP has been described. The duration of follow up of 12.2 months in this study may appear short, and a longer follow up might have shown higher figures for progression. However, the progression of RAP to CP in a statistically significant number of patients clearly suggests that this short period was adequate to assess such progression. A longer term follow up of patients with idiopathic and alcoholic pancreatitis could potentially have led to different conclusions. Previous studies have shown progression in idiopathic, alcoholic and hereditary pancreatitis from the Western world [27, 28]. Our results demonstrate that idiopathic CP in patients from southern India evolves similarly through a phase of RAP. The delay from the onset of symptoms to diagnosis in early- and late-onset idiopathic and alcoholic CP recently reported from southern India, thus appearing to be accounted at least partly by the lack of telltale imaging findings of CP or exocrine and endocrine insufficiency, when the patients pass through the phase of RAP and early CP [14]. Our findings also assume importance in the light of the evolving disease pattern in CP reported from southern India and the attendant questioning of the very existence of the entity of TCP [12–15].

Previous studies have shown progression of AP to CP over time in varying proportions in the alcoholic or idiopathic subgroups; this being much more likely after a second episode of pancreatitis occurred [3, 4, 29, 30]. Such variability in progression appears to be due to the differences in the mix of patients studied and the duration of follow up. Broadly,

Table 2 Comparison of stool fat, fasting blood sugar and visual analogue scale at baseline and on follow up in patients with recurrent acute who progressed to chronic pancreatitis and in those who did not progress

Variable	RAP who progressed to CP (n = 07)		RAP who did not progress to CP (n = 37)	
	Baseline	Follow up	Baseline	Follow up
Stool fat (mean ± SD)	6.6 ± 0.33	6.6 ± 0.70	6.1 ± 0.85	6.2 ± 0.35
FBS (median [IQR])	92.0 (84.0, 98.0)	86.0 (81.0, 92.0)	87.0 (83.5, 96.5)	91.0 (84.0, 97.5)
VAS (median [IQR])	06.0 (03.0, 09.0)	05.0 (0, 08.0)	6.0 (4.0, 8.2)	2.7 (0, 5.5)*

Significance level at $p < 0.05$ *$p = 0.001$ by two-way Friedman's test, for RAP patients who did progress to CP, compared at baseline and follow up

FBS fasting blood sugar, *VAS* visual analogue scale, *IQR* interquartile range

progression was seen more often in alcoholic (16 % to 48 %) compared to idiopathic pancreatitis (0 % to 13 %) [3, 4, 29, 30]. On the other hand, nearly half the patients with idiopathic RAP progressed to CP over 8 years in a previous study from India, irrespective of the presence of and treatment for biliary microcalculi at baseline [31]. Clearly, CP—at least some etiological subgroups of it—should be considered as a disease continuum with RAP. Studies on histology and on the genetic basis of RAP and CP additionally support this [15, 32, 33]. Accordingly, Schneider et al. have developed a staging system for CP which includes AP and RAP as the earlier stages of this disease [34].

Among the 7 patients who progressed from RAP to CP, 3 (6.8 %) developed exocrine insufficiency. The presence of steatorrhea in 4.5 % of patients with RAP at baseline may appear unusual, but this was found to reverse during follow up and can be attributed to the transient reduction in pancreatic function during an acute episode of inflammation [35]. Similarly, DM was seen in 9 % with RAP and none of the patients developed changes of CP during follow up, suggesting that the former condition was idiopathic and not secondary to pancreatitis [36]. DM is quite prevalent in India, may be incidentally present in a patient who develops AP or may even predispose to the same [37, 38]. Clearly, the suggestion that the presence of DM or steatorrhea be used as evidence for CP in patients with RAP is open to question [39, 40].

The time interval to the development of DM and pancreatic exocrine insufficiency may vary with the type of pancreatitis, study design, duration of follow up and the tests used [1]. Exocrine insufficiency and DM occurred earlier in those with alcoholic pancreatitis and late-onset ICP as compared to early-onset ICP, whereas these features were reported in up to 70 % in tropical pancreatitis at the time of presentation [1, 14, 41]. More recently, pancreatic exocrine insufficiency have been noted in 34.4 % and 53.2 % in early- and late-onset ICP, respectively [14]. These lower figures for exocrine and endocrine insufficiency in recent reports on CP, including ours, may reflect the diagnosis of CP in earlier stages [14].

The significant reduction in the severity of pain in our patients with RAP during follow up was presumably due to the therapeutic interventions in them, although there is no conclusive evidence in the literature to confirm the usefulness of such therapy in this condition. The similar improvement seen in pain as well as stool fat excretion in CP could also be attributed to the therapeutic interventions in these patients. Patients with CP with repeated hospitalization for flares of abdominal pain have been shown to develop exocrine insufficiency faster [42]. While enzyme replacement therapy improves steatorrhea in CP, its role in the management of pain is questionable, as is the role of supplementation of anti-oxidants [43–46]. Endoscopic pancreatic stenting is effective in relieving pain in patients with CP but has not been shown to

Table 3 Comparison of stool fat, fasting blood sugar and visual analogue scale at baseline and on follow up in patients with chronic pancreatitis who progressed and in those who did not progress

Variable	CP who progressed (n = 19)		CP who did not progress (n = 77)	
	Baseline	Follow up	Baseline	Follow up
Stool fat (mean±SD)	8.3 ± 2.8	7.9 ± 1.7	8.9 ± 3.3	7.4 ± 1.5*
FBS (mean±SD)	97.8 ± 27.8	105.5 ± 34.8	112.1 ± 50.0	114.3 ± 68.7
VAS (median [IQR])	6.2 (4.0, 8.0)	4.2 (1.0, 6.3)	6.0 (4.0, 8.0)	2.7 (0.0, 5.5)**

Significance level at $p < 0.05$ *$p < 0.001$ by repeated measures ANOVA; **$p < 0.001$ by two-way Friedman's test for CP patients who did not progress compared at baseline and follow up

CP chronic pancreatitis, *FBS* fasting blood sugar, *VAS* visual analogue scale, *IQR* interquartile range

improve the exocrine and endocrine dysfunction [24, 47]. Our study, while not specifically designed to answer these questions, suggests that there may be subgroups of patients who show improvement in pain and prevent further progression in RAP and CP with appropriate interventions. Well-designed, long-term studies are needed to elucidate these results further.

The use of different imaging techniques in addition to USG to diagnose CP might appear to be a limitation of our study. While the four imaging options other than USG admittedly have slightly differing sensitivities, none are considered the gold standard and there are no head to head comparisons of all four imaging techniques for the diagnosis of CP [22]. When USG, which has a sensitivity of 60 % to 80 % [20, 22], clearly showed evidence of CP, we did not do further imaging studies. This approach is supported by recent guidelines [20–22] as well as the recommendation by the Rosemont group that EUS findings 'suggestive of CP' would need additional testing for the confirmation of CP [23]. The fact that all 7 patients with RAP who progressed to CP had undergone EUS at baseline evaluation and that CP was diagnosed at follow up in them based on findings 'consistent with CP' should nullify the effect of the differing sensitivities of the different modalities at least in this subgroup.

Some studies have prescribed a high-fat diet prior to stool fat estimation by the acid steatocrit method, while others have not, still providing sensitivity, specificity and positive predictive values between 90 % and 100 % [48–50]. We did not advice any dietary changes prior to the acid steatocrit test nor was enzyme replacement discontinued as this would have been ethically inappropriate.

In summary, 15.9 % of patients diagnosed with RAP progressed to CP over a median time of 20.0 months, this being commoner in the idiopathic compared to the alcoholic subgroup. Progression of CP over time occurred similarly in the idiopathic (20.8 %) and alcoholic (16.6 %) subgroups. Our data provide additional evidence for the progressive spectrum constituted by idiopathic RAP and CP during a short-term follow up in patients from southern India.

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Compliance with ethical standards

Conflict of interest MGK, CGP, and AK declare that they have no conflict of interest.

Human and animal rights and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2008. We obtained informed consent from individual patients and Institutional ethics committee clearance was obtained.

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