Progression of alcoholic acute to chronic pancreatitis

R W Ammann, B Muellhaupt

Abstract
Alcoholic chronic pancreatitis usually progresses from acute attacks to chronic pancreatitis within one to 19 years. The factors responsible for the appreciable variability in progression are unclear. In this study the relation between progression and the incidence and severity of acute episodes in a large cohort of patients with alcoholic chronic pancreatitis was analysed. All patients with at least one documented episode of acute pancreatitis have been studied prospectively over the past 30 years according to our protocol. Patients were classified according to their long term course into (a) calcific (n=185), (b) non-calcific (n=30), and (c) non-progressive (n=39) chronic pancreatitis groups. The yearly incidence of acute attacks of pancreatitis was significantly higher in groups (a) and (b) than in group (c). Furthermore, the progression rate to advanced chronic pancreatitis (groups (a) and (b)) correlated with the incidence of severe pancreatitis (associated with pseudocysts in more than 55%). Pseudocysts were located primarily in the cephalic pancreas in groups (a) and (b) (58–71%) and in the pancreatic tail in group (c) (61%). In conclusion, these data suggest that the progression of acute to chronic pancreatitis is closely related to the incidence and severity of acute attacks. This finding and the primary location of pseudocysts in the cephalic pancreas (groups (a) plus (b)) are compatible with the 'necrosis-fibrosis' pathogenetic hypothesis.

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The relationship between acute and chronic pancreatitis has long been debated. In 1946, Comfort et al suggested that chronic pancreatitis was the consequence of repeated attacks of acute pancreatitis.1 This hypothesis was based on a long term study of 29 patients with recurrent alcoholic (or non-biliary) pancreatitis. In the early 60s, Sarles et al postulated that chronic pancreatitis could hardly be the consequence of acute pancreatitis since patients with this disorder were a mean of 13 years older when they had their first attack and more women than men were affected.2 Sarles’s series of acute pancreatitis, however, was based primarily on patients with biliary (or non-alcoholic) pancreatitis. Since the classic published reports of Howard and Ehrlich3 and Marks et al,4 the differences in the natural histories of biliary and alcoholic pancreatitis have been generally recognised. Nevertheless, in the definitions of Marseille meetings (in 1963 and 1984), the aetiology was not considered an important factor in terms of the outcome of pancreatitis.4 Thus, for the past 30 years acute and chronic pancreatitis have been separated into two distinct entities irrespective of aetiology.5 Much confusion has resulted from the authoritative statement of the two Marseille meetings that progression of acute to chronic pancreatitis is extremely uncommon.6 Alcohol abuse is the most common cause of chronic pancreatitis in western countries. The natural history of alcoholic chronic pancreatitis is characterised by recurrent episodes of pancreatitis in the early stages and by progressive pancreatic dysfunction, often associated with calcification, in the late stages.78 Some experts assume that alcoholic ‘acute’ pancreatitis occurs regularly on the basis of pre-existent, clinically latent chronic pancreatitis.910 This hypothesis has been challenged recently by a prospective long term study which indicated that about 30% of patients with recurrent alcoholic pancreatitis did not progress to advanced chronic disease.10

The pathogenesis of chronic pancreatitis is still obscure. There have been various suggestions, most notably the ‘toxic-metabolic’ and the ‘protein-plug’ hypotheses.11 Klöppel and Maillet recently made a further proposition, based on histopathology, that chronic pancreatitis may develop as a late sequela of necrotising pancreatitis12 (Fig 1). We tested this ‘necrosis-fibrosis’ hypothesis using data from our prospective long term study of alcoholic chronic pancreatitis.12 In particular, the incidence and severity of acute attacks of alcoholic pancreatitis were analysed, based on the hospital records in well defined cohorts of patients with calcific, non-calcific, and non-progressive chronic pancreatitis.12

DEFINITIONS
The duration of disease is the time between onset (first typical episode of pancreatitis) and either the cut off point (June 1992), the last personal contact, or the death of the patient. The course of the disease up to the first personal contact (equal to entry) was analysed, based on hospital records. The patients were studied prospectively at regular intervals from entry until the last contact (equal to follow up time) according to our protocol.4 Alcohol was considered a cause in patients who had consumed ≥80 g pure ethanol daily for at least five years.

The diagnosis of advanced chronic pancreatitis was based upon a typical history and on one or more of the following:

1. Pancreatic calcification seen on x ray;6
2. Typical pancreatic histology; associated with persistent exocrine insufficiency (faecal chymotrypsin <120 µg/g for at least two years);7
3. Persistent exocrine insufficiency or pancreatic steatorrhea, or both (>7 g/24 h; chymotrypsin <7.5 mg/24 h).

A diagnosis of non-progressive chronic pancreatitis was based on a typical history of
Progression of alcoholic acute to chronic pancreatitis

(1) Calcific chronic pancreatitis (n = 185) (CCP);
(2) Non-calcific chronic pancreatitis (n = 30) (NCP);
(3) Non-progressive chronic pancreatitis (n = 39) (NPCP).

Seven additional patients in the last group were excluded because of a duration of disease of six or fewer years.

All hospital, surgical, histopathological, and autopsy records of each patient were reviewed retrospectively to assess the incidence and severity of acute pancreatitis and its complications. The diagnosis of acute pancreatitis was based on a consistent clinical picture associated with an appreciable documented increase in pancreatic serum enzyme activities (three or more times the upper limit). Pain episodes without laboratory confirmation were only considered as acute attacks in patients with typical clinical findings, one to several documented previous episodes of pancreatitis, and without an extrapancreatic cause of epigastric pain. The severity of attacks was graded as mild or severe. There are no generally accepted criteria to define severe attacks, and different classifications have been described. For the present study attacks of pancreatitis were considered severe if one or more of the following criteria were fulfilled:

(1) Local complications existed, such as pseudocysts, abscesses;
(2) Systemic complications, for example, shock, pulmonary complications with hypoaemia or radiological signs, or both, renal failure;
(3) Metabolic disturbance such as transient hyperglycaemia/glycosuria or marked hypo- calcaemia existed;
(4) Patients were in hospital for >15 days.

The proportion of severe attacks in the present series was about 30%, which is comparable with the current published reports.4 Severe attacks were associated with pseudocysts (or abscesses) in 55–66% of patients. The diagnosis of pseudocysts or abscesses was established primarily by ultrasound, CT, or ERCP and was confirmed by surgery. The pseudocysts occurred primarily within the first six years from onset (>85%) in association with acute pancreatitis (that is, most were probably post-necrotic cysts).

The rate of attacks of pancreatitis in the three subgroups was calculated on a yearly basis. The incidence of attacks was considered in the NPCP group for the whole duration of disease, in the CCP and the NCP groups, however, only the time from onset to the diagnosis of chronic pancreatitis was included.

The statistical analysis for these unpaired non-parametric data was performed with the Kruskal-Wallis (three groups or more) or the Mann-Whitney U test (two groups). For all studies, a p value <0.05 was considered statistically significant. The values of all variables are expressed as mean (SD).

Results

The relevant clinical data for the 254 patients are summarised in Table I. CCP was the largest...
group by far, while the NCP and NPCP groups were comparable in size. In all three groups, the sex and age distributions were about equal (Table I). The time of follow up was similar in the three groups, but the duration of disease was significantly longer in the CCP group than in the other two (Table I). The diagnosis of chronic pancreatitis was established 4-8 (3-8) years from onset in the CCP group and 5-4 (4-8) years from onset in the NPCP group (NS).

The incidence of acute attacks of pancreatitis (mild and severe) was significantly higher in the CCP than in the NCP and NPCP groups (Table II). No significant difference was noted between the NCP and NPCP groups (Table II). The incidences of severe attacks were similar in the CCP and NCP groups but significantly lower in the NPCP group (Table II).

The incidence of pseudocysts did not differ significantly between the three subgroups, even though it was almost double in the CCP and NCP groups compared with the NPCP group (Table III). Interestingly, the pseudocysts occurred primarily in the cephalic pancreas in the CCP (71%) and the NCP groups (58%), but in the NPCP group 61% originated in the pancreatic tail (Table III).

The progression rate in advanced chronic pancreatitis was closely related to the incidence of severe attacks of pancreatitis, that is the shorter the time between the onset and diagnosis of chronic pancreatitis the greater the incidence of severe pancreatitis (Fig 2).

Discussion
The results of the present study suggest that progression (or non-progression) of alcoholic pancreatitis to advanced chronic disease is determined primarily by two factors – the incidence and severity of acute attacks of pancreatitis and the localisation of necrosis (that is, pseudocysts) within the cephalic portion of the pancreas. These data are at variance with the current view that virtually no transition exists between acute and chronic pancreatitis.5

SHORT TERM STUDIES AFTER ACUTE (ALCOHOLIC) PANCREATITIS
Increasing evidence for a transition from acute to chronic pancreatitis has been presented in recent years. In several prospective short term studies, functional impairment or persistent morphological changes (on ERCP), or both, have been noted after acute pancreatitis in man.17-21 Full recovery of exocrine function may not occur within four years of onset, depending on the severity of the acute pancreatitis.22 Similar results were reported for the recovery of endocrine function.23 On ERCP, moderate or severe ductal changes compatible with chronic pancreatitis after necrohaemorrhagic pancreatitis were noted in about 50% of patients in one study, but no progression of these changes occurred during the four years of follow up.24 In some series, the functional and morphological changes were more pronounced after alcoholic than biliary pancreatitis.25 Whether or not these changes in function and morphology were the first evidence of progression to chronic pancreatitis cannot be resolved because of the short follow up (four or fewer years).26 However, these data suggest a broad overlap between acute and chronic pancreatitis, particularly in the early phase after alcoholic pancreatitis.

LONG TERM STUDIES: ALCOHOLIC CHRONIC PANCREATITIS IN RELATION TO INCIDENCE, SEVERITY OF ACUTE PANCREATITIS, AND PSEUDOCYSTS
There are only few prospective clinical long term studies of alcoholic acute pancreatitis (five years or longer) and the data are controversial. According to Gullo et al., alcoholic pancreatitis regularly progresses to advanced chronic pancreatitis, but progression may be delayed in patients who have stopped abusing alcohol.27 In accordance with these results, most patients with alcoholic pancreatitis in the present series progressed to advanced chronic disease (Table I). A subgroup of patients, however, did not develop the hallmark of advanced disease irrespective of alcohol intake (NPCP). This subgroup may be identical with 'small-duct' chronic pancreatitis, an ill defined entity mentioned mainly in surgical

Table I: Relevant clinical data in patients with chronic pancreatitis (CP)

<table>
<thead>
<tr>
<th></th>
<th>Calcific CP (CCP)</th>
<th>Non-calcific CP (NCP)</th>
<th>Non-progressive CP (NPCP)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>185</td>
<td>10</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>8/7</td>
<td>5/1</td>
<td>3/5</td>
<td></td>
</tr>
<tr>
<td>Age at onset (y):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>38-37 (10-65)</td>
<td>20-70</td>
<td>55-49</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>33-69 (7-5)</td>
<td>22-63</td>
<td>25-55</td>
<td></td>
</tr>
<tr>
<td>Follow up (y):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10-28 (3-6)</td>
<td>0-20</td>
<td>2-25</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>10-32 (1-17)</td>
<td>3-25</td>
<td>1-25</td>
<td></td>
</tr>
<tr>
<td>Duration of disease (y):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13-37 (6-18)</td>
<td>1-37 (1-23)</td>
<td>11-33 (5-16)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>13-37 (6-18)</td>
<td>1-37 (1-23)</td>
<td>11-33 (5-16)</td>
<td></td>
</tr>
</tbody>
</table>

Table II: Incidence of acute attacks of pancreatitis in the three groups of patients with chronic pancreatitis (CP)

<table>
<thead>
<tr>
<th>Acute attacks</th>
<th>Calcific CP (CCP)</th>
<th>Non-calcific CP (NCP)</th>
<th>Non-progressive CP (NPCP)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no (mild/severe): Mean (SD)</td>
<td>1-37 (1-17)</td>
<td>1-02 (1-32)</td>
<td>1-26 (0-19)</td>
<td>CCP/NCP&lt;0-05 CCP/NCP&lt;0-01 NPCP/NPCP NS</td>
</tr>
<tr>
<td>Range</td>
<td>6-9</td>
<td>0-04-7-0</td>
<td>0-06-1-0</td>
<td></td>
</tr>
<tr>
<td>Severe attacks: Mean (SD)</td>
<td>0-44 (0-54)</td>
<td>0-43 (0-39)</td>
<td>0-11 (0-13)</td>
<td>CCP/NCP&lt;0-05 CCP/NCP&lt;0-01 NPCP/NPCP NS</td>
</tr>
<tr>
<td>Range</td>
<td>0-4</td>
<td>0-01-67</td>
<td>0-0-5</td>
<td></td>
</tr>
</tbody>
</table>

Table III: Incidence and location of pseudocysts in the three groups of patients with chronic pancreatitis (CP)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Calcific CP (CCP)</th>
<th>Non-calcific CP (NCP)</th>
<th>Non-progressive CP (NPCP)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no: Mean (SD)</td>
<td>1-37 (1-23)</td>
<td>1-01 (0-16)</td>
<td>0-06 (0-09)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-1</td>
<td>0-05</td>
<td>0-38</td>
<td></td>
</tr>
<tr>
<td>Location of pseudocysts (on %): Head/body</td>
<td>49 (21)</td>
<td>7 (58)</td>
<td>5 (28)</td>
<td></td>
</tr>
<tr>
<td>Tail</td>
<td>16 (23)</td>
<td>3 (25)</td>
<td>10 (61)</td>
<td></td>
</tr>
<tr>
<td>Unknown or extrapancreatic</td>
<td>3 (6)</td>
<td>1 (17)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Total no</td>
<td>68 (100)</td>
<td>12 (100)</td>
<td>17 (100)</td>
<td></td>
</tr>
</tbody>
</table>

In the CCP and NCP groups only pseudocysts which occurred before the diagnosis of CP are considered. Infected pseudocysts and postnecrotic abscesses are included in these figures.
published reports, which does not progress to advanced ('large-duct') chronic pancreatitis.\textsuperscript{21}

These data suggest that the progression (or non-progression) of alcoholic pancreatitis to advanced chronic pancreatitis is correlated with the total incidence of acute attacks of pancreatitis (mild and severe) (Table II). In addition, a significant difference in the incidence of severe acute pancreatitis and the final outcome was found between the CCP and NCP groups and the NCP group (Table II). Furthermore, the rate of progression to CCP and NCP correlated with the incidence of severe attacks of pancreatitis (Fig 2). It may be argued that the severity grading of acute attacks on the basis of a retrospective review of hospital records was rather imprecise. It is obvious that the available clinical, morphological, and biological data did not permit the application of a sophisticated score index as designated by some experts.\textsuperscript{19} However, the grading system was probably appropriate, which is supported by the fact that over 55% of patients with severe acute pancreatitis developed (probably postnecrotic) pseudocysts or abscesses.

The incidence of pseudocysts in the three groups was not significantly different (Table III). It should be noted, however, that the pseudocysts were primarily located in the cephalic pancreas in the CCP and NCP groups and in the pancreatic tail in the NCP group (Table III). This is in accordance with the results of some large series of patients with alcoholic chronic pancreatitis in whom pseudocysts were found more often in the head or body (75–88%) than in the tail of the pancreas (10–14%).\textsuperscript{24,25} It is possible that in patients with cephalic pseudocysts, postnecrotic fibrosis induces obstruction of the pancreatic ducts which causes progressive upstream acinar destruction and fibrosis as suggested in the 'necrosis-fibrosis' hypothesis\textsuperscript{26} (Fig 1). This assumption is supported by recent animal studies of bile salt-induced acute pancreatitis in rats.\textsuperscript{27} In these experiments persistent chronic pancreatic lesions were observed focally in those lobules which were drained by large pancreatic ducts obstructed by fibrosis.\textsuperscript{28} Such a mechanism may also be implicated in some patients with postnecrotic, non-alcoholic chronic pancreatitis.\textsuperscript{29}

It seems less likely that the 'necrosis-fibrosis' hypothesis is also applicable to primary painless chronic pancreatitis because extensive necrosis associated with acute pancreatitis does not usually occur without severe clinical symptoms such as abdominal pain, shock, or multi-organ failure. Therefore, 10% of patients with painless alcoholic chronic pancreatitis were excluded from this series (see Methods). According to some experts, alcoholic acute pancreatitis is regularly superimposed on clinically latent chronic pancreatitis.\textsuperscript{30,31} Since no histology at onset of 'acute' pancreatitis is available in the present series, this thesis cannot be disproved. However, in a recent autopsy series of 247 patients with fatal acute alcoholic pancreatitis, 53% of cases had histologically acute pancreatitis unassociated with chronic changes.\textsuperscript{32}

Accordingly, these data challenge the Marseille classification which negates the transition from acute to chronic pancreatitis. This seems to be true for gall stone pancreatitis, but is obviously unlikely for alcoholic pancreatitis.

Additional prospective long term studies in large series of patients with acute pancreatitis with well defined severity are necessary to confirm (or refute) our findings. Future research regarding the pathophysiology of chronic pancreatitis should take into account the facts that there are probably:

1. Different subgroups of chronic pancreatitis (for example, alcoholic \& non-alcoholic chronic pancreatitis; progressive \& non-progressive chronic pancreatitis; and chronic pancreatitis with recurrent attacks of pancreatitis \& primary painless chronic pancreatitis).

2. Probably more than one pathogenetic mechanism for chronic pancreatitis.

As emphasised in a recent review, a combination of the different postulated pathogenetic mechanisms – primarily 'toxic', 'protein-plug', and 'necrosis-fibrosis' hypothesis – may be active in chronic pancreatitis.\textsuperscript{32}

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1 Comfort MW, Gambill EE, Baggenstos AH. Chronic relapsing pancreatitis: a study of 29 cases without associated disease of the biliary or gastro-intestinal tract. Gastroenterology 1946; 6: 239–85 and 376–408.


