Are the causes similar for benign and severe forms of acute pancreatitis?

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SUMMARY
The frequency of severe acute pancreatitis not due to alcohol or biliary causes is not well known.

Aims — To evaluate the distribution of causes responsible for benign and severe cases of acute pancreatitis in an effort to identify causes to search for in patients with severe acute pancreatitis.

Patient — All patients hospitalized for acute pancreatitis between January 1994 and May 2001 with a good quality CT scan.

Methods — All patients had a complete, standardized evaluation to look for all possible causes of acute pancreatitis. The following severity criteria were retrospectively reviewed: maximal C-reactive protein level, Ranson’s score, Balthazar’s score, percentage of patients hospitalized in intensive care unit or a high-dependency unit, hospitalization duration, and local or general complications.

Results — One hundred thirty-nine patients were included. The cause of acute pancreatitis was: alcohol (34%), biliary (27%), obstructive (16%), miscellaneous (10%), unknown (9%), post endoscopic retrograde cholangio-pancreatography (4%). The studied severity factors did not differ with respect to the cause of acute pancreatitis with the exception of Balthazar’s score. Non-alcoholic non-biliary causes were found in 19 (27%) of the 71 patients with severe necrotic acute pancreatitis (Balthazar ≥ D) and 35 (51%) of the 68 patients with acute pancreatitis with Balthazar score < D (P < 0.009).

Conclusion — Non-alcoholic and non-biliary causes are less frequent in necrotizing pancreatitis (Balthazar ≥ D). For the other severity scores, the distribution of causes was similar. After exclusion of biliary and alcoholic causes, a careful search for other etiologies should be carried out in both benign and severe cases of acute pancreatitis.

Acute pancreatitis is not uncommon in France with an incidence of 22: 100,000. The prognosis varies and ranges from benign to severe [1]. Chronic alcohol abuse and biliary lithiasis are the leading causes and are responsible for 70% and 80% of cases, respectively [2, 3]. Acute pancreatitis due to non-alcoholic (non-A) and non biliary (non-B) causes, e.g. tumor-related ductal obstruction, may require specific treatment or measures and must not be confused with idiopathic acute pancreatitis.

The similar clinical, biological, and radiological expression, and short-term prognosis, of acute pancreatitis makes it difficult to distinguish between the wide range of underlying conditions. Furthermore, non-A non-B AP is infrequent and little is known concerning its severity and prognosis. There has been much

RÉSUMÉ
Les pancréatites aiguës bénignes et sévères ont-elles les mêmes causes ?

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La fréquence, voire l’existence, des pancréatites aiguës sévères d’origine non alcoolique et non bilaire est discutée.

Buts — Comparer la répartition des causes parmi les pancréatites aiguës bénignes et sévères afin de déterminer les causes à chercher devant une pancréatite aiguë sévère.

Maladies — Tous les malades hospitalisés pour une pancréatite aiguë entre janvier 1994 et mai 2001 et ayant eu une scannographie de bonne qualité.

Méthodes — Tous les malades avaient un bilan standardisé et exhaustif à la recherche des causes potentielles. Les critères de sévérité suivants étaient étudiés rétrospectivement : pic de protéine C-réactive, score de Ranson, score de Balthazar, pourcentage de malades hospitalisés en réanimation ou en chirurgie, durée d’hospitalisation, complications locales ou générales.

Résultats — Cent trente-neuf malades étaient inclus. La fréquence des causes était : alcoolique (34 %), bilaire (27 %), obstructive (16 %), diverses (10 %), indéterminées (9 %) et post-cholangiopancréatographie endoscopique (4 %). Il n’existait aucune différence significative de la répartition de chaque cause pour les critères de gravité étudiés sauf pour le score de Balthazar : les pancréatites non alcooliques non biliaires représentaient 19 (27 %) des 71 pancréatites avec un score ≥ D et 35 (51 %) des 68 ayant un score < D (P < 0,009).

Conclusion — Les pancréatites non alcooliques non biliaires sont moins fréquentes dans le groupe des pancréatites nécrosantes (score de Balthazar ≥ D), mais elles représentent malgré tout plus d’un quart des cas de ces dernières. Pour les autres critères de gravité, il n’y a pas de différence de répartition des causes selon que ce critère est présent ou non. La recherche des causes non alcooliques non biliaires doit être effectuée aussi bien dans les formes sévères que dans les formes bénignes.
discussion on whether severe non-A non-B acute pancreatitis is a real clinical entity. If one accepts that severe forms of non-A non-B acute pancreatitis exists then its prevalence also remains to be determined. This leads to question the usefulness of an exhaustive etiological work-up.

The purpose of this work was to compare the distribution of the underlying causes observed in patients with severe and benign acute pancreatitis as defined by recognized criteria, in order to determine which causes should be searched for in patients with severe acute pancreatitis. In our unit, the proportion of patients with acute pancreatitis due to chronic alcohol consumption or biliary lithiasis is lower than generally reported, giving us the opportunity to study a subpopulation with more exceptional causes of acute pancreatitis.

Patients and methods

Patients

This retrospective analysis concerned all patients hospitalized in the gastroenterology unit of Beaujon Hospital between January 1994 and May 2001 for acute pancreatitis or complications of acute pancreatitis. Some patients had been hospitalized in other institutions prior to referral.

Inclusion criteria

Patients presenting an episode of acute pancreatitis defined as a painful abdominal syndrome compatible with a pancreatic origin and requiring hospitalization, associated with elevated serum lipase and/or serum amylase and/or urinary amylase = 3 times the upper limit of normal [N] were included in the study [4].

Exclusion criteria

Patients were excluded if the medical files provided incomplete information with respect to disease severity or cause of acute pancreatitis or if an abdominal computed tomography (CT) scan had not been performed within 72 hours of admission.

Methods

Study parameters

Data were collected from the medical files of the units where the patients had been hospitalized (Gastroenterology Unit of Beaujon hospital, other institutions). If the cause of acute pancreatitis was unclear, the case was discussed during a multidisciplinary meeting between gastroenterologists, surgeons, and radiologists. General parameters studied were cause of acute pancreatitis, patient age and gender, and length of hospital stay. Severity criteria were noted for each patient and divided into two categories:

1. A priori criteria predictive of severity: maximal C-reactive protein (CRP) and number of patients with CRP > 120 mg/l [7,9], Ranson’s clinical-biological score [10];
2. A posteriori criteria defined according to the Atlanta classification [6] by the presence of local or general complications, i.e. Balthazar score = D (necrotizing pancreatitis) [11-13], presence or absence of superinfection, pseudocyst measuring ≥ 2 cm, pancreatic fistula, intra-pancreatic bleeding, SOFA score (sepsis-related organ failure) at least one organ [14], at least one episode of generalized sepsis, need for emergency surgery to treat complications of acute pancreatitis, or acute pancreatitis-related death.

Severe acute pancreatitis was defined as the presence of one or more of these criteria. The following data were also noted: proportion of patients admitted to digestive surgery and intensive care for complication of acute pancreatitis, length of hospital stay in digestive surgery and intensive care.

ETIOLOGICAL DIAGNOSIS

— Alcoholic acute pancreatitis: alcohol consumption > 60 g/d for more than 2 years [16] with no other argument in favor of a biliary or other cause;
— Biliary acute pancreatitis: presence of a stone in the gallbladder or bile ducts identified at ultrasonography, small stone or sludge in the gallbladder or main bile duct identified at endoscopic biliopancreatic ultrasonography performed outside a period of fasting and without chronic alcohol abuse with no other argument favoring another cause;
— Other causes of acute pancreatitis including obstruction, endoscopic retrograde cholangiopancreatography (ERCP), miscellaneous: history (trauma, operation, ERCP), clinical findings, laboratory results (genetic mutation, hypertriglyceridemia), morphology (tumor), histology, clinical course [15]. Obstructive acute pancreatitis included ductal pancreatitis due to a pancreatic tumor (adenocarcinoma, cyst, intraductal papillary and mucinous tumor, endocrine tumor, papillary adenoma), and acute pancreatitis associated with duodenal diverticula(e), pancreas divisum, sphincter of Oddi dysfunction, stricture of a pancreatogastric anastomosis;
— Acute pancreatitis of undetermined origin: all of the preceding causes ruled out [15].

Statistical analysis

Analysis of variance (ANOVA) was used to compare quantitative variables, and the chi-square test to compare qualitative variables. P < 0.05 was considered significant. Results are expressed as mean ± standard deviation or in absolute value (percentage).

Results

Study population

One hundred thirty-nine patients (75% men) were included in the study. Mean age was 46 ± 15.6 years. The cause of acute pancreatitis was alcohol abuse (n = 47), biliary lithiasis (n = 38), obstruction (n = 22), other (n = 14): hypertriglyceridemia (n = 3), autoimmune disease (n = 3), hereditary disease (n = 3), surgery or migration of a biliary prosthesis (n = 2), cystic fibrosis (n = 1), eosinophil pancreatitis (n = 1), trauma (n = 1), ERCP (n = 6), undetermined (n = 12). Patients with non-A non-B acute pancreatitis accounted for 39% of the study population. Mean length of hospital stay was 29 ± 44 days.

The distribution by cause (table I) was significantly different for age (P < 0.0001) and gender (P < 0.015). There was no significant difference between the different causes of acute pancreatitis for the other general characteristics.

Criteria of severity

A PRIORI CRITERIA (CRITERIA PREDICTIVE OF SEVERITY)

Maximal serum CRP was available for 93 patients (67%). The mean peak was 117 ± 126.2 mg/l. CRP was = 120 mg/l in 38 patients.

| Table I. — Distribution of age and sex for each cause. |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Alcohol Biliary Obstruction Misc. Undetermined ERCP |
| Mean age, yrs | 43 | 55 | 52 | 30 | 40 | 49 |
| [SD] | [7.3] | [18.3] | [13.1] | [14.9] | [13.1] | [15.4] |
| men, n | 38 | 21 | 12 | 10 | 7 | 1 |
| (% | [81] | [55] | [55] | [71] | [58] | [17] |

ERCP: endoscopic retrograde cholangiopancreatography; SD: standard deviation.
The differences are significant for age (P < 0.0001) and sex (P < 0.015)
Inevitable biases which could influence the distribution of causes and severity of acute pancreatitis in one way or another. The unusually large proportion (39%) of patients with non-A non-B acute pancreatitis might have resulted from the fact that our unit is a referral center for regional institutions. Furthermore, certain data, e.g. CRP level or laboratory results needed to calculate the Ranson score, were missing in certain patient files. We used the Balthazar score described in 1985 [11] instead of the amended score described in 1990 [12] to facilitate a more accurate retrospective analysis, particularly because a CT-scan was not always performed under standard conditions. Referral practices may have increased the number of patients with severe clinical presentations, notably necrotizing pancreatitis. Inversely, exclusion of patients without a CT-scan or who had not been hospitalized might have lowered the number of patients with benign pancreatitis.

Are the causes similar for benign and severe forms of acute pancreatitis?

### Table II. Distribution of causes among all patients with acute pancreatitis, among those with Balthazar’s score ≥ D and those with a pseudocyst.

<table>
<thead>
<tr>
<th>Cause of acute pancreatitis</th>
<th>Cause of acute pancreatitis (% among all patients)</th>
<th>Cause of acute pancreatitis (% among patients with Balthazar score ≥ D)</th>
<th>Cause of acute pancreatitis (% among patients with pseudocyst)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 139 (n %)</td>
<td>n = 71 (n %)</td>
<td>n = 26 (n %)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>34 (25%)</td>
<td>30 (42%)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Biliary</td>
<td>38 (27%)</td>
<td>22 (31%)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>non A non B (total)</td>
<td>54 (39%)</td>
<td>19 (27%)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>• Obstruction</td>
<td>22 (16%)</td>
<td>4 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>• Other</td>
<td>14 (10%)</td>
<td>7 (10%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>• Unknown</td>
<td>12 (9%)</td>
<td>4 (6%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>• ERCP</td>
<td>6 (4%)</td>
<td>4 (6%)</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

AP: acute pancreatitis; non A non B: non alcoholic non biliary; ERCP: endoscopic retrograde cholangiopancreatography

<table>
<thead>
<tr>
<th>Cause</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>47 (34%)</td>
</tr>
<tr>
<td>Biliary</td>
<td>38 (27%)</td>
</tr>
<tr>
<td>non A non B total</td>
<td>54 (39%)</td>
</tr>
<tr>
<td>• Obstruction</td>
<td>22 (16%)</td>
</tr>
<tr>
<td>• Other</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>• Unknown</td>
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</tr>
<tr>
<td>• ERCP</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>

The Ranson score was available for 120 patients (86%) and was = 3 in 13 (11%). The Balthazar score was available for all patients and was = D in 71 (51%).

### A posteriori criteria

Twenty-two percent of the patients were admitted to a surgical ward and 24% and to intensive care. Mean hospital stay in surgery and intensive care was 14 ± 30 days respectively. At least one pseudocyst measuring = 2 cm was observed in 26 patients (19%), pancreatic complication (excepting pseudocyst) in 18 (13%), organ failure in 29 (21%), and sepsis in 31 (22%). Surgery was needed to treat complications of acute pancreatitis in 57 patients (41%) including 15 (11%) who underwent an emergency procedure. Two patients (1.2%) died from multiple-organ failure secondary to superinfection of pancreatic necrosis; both had alcoholic acute pancreatitis.

### Distribution by cause of benign and severe acute pancreatitis

Analysis of the criteria of severity (data not shown) did not demonstrate any significant difference in the distribution by cause, except for Balthazar score: non-A non-B pancreatitis was diagnosed in 19 of the 71 patients (27%) with a Balthazar score = D and in 53 of the 68 patients (86%) with a Balthazar score < D (P = 0.009) (table II). The distribution of the causes in patients with pseudocysts exhibited a difference close to significance (P = 0.057): 9 of the 26 patients (35%) with pseudocysts had non-A non-B pancreatitis versus 45 of the 113 patients (40%) without pseudocysts (P = 0.057) (table II). Fifteen to 50% of patients with other criteria of severity had non-A non-B pancreatitis.

### Discussion

This retrospective monocentric study has a certain number of inevitable biases which could influence the distribution of causes and severity of acute pancreatitis in one way or another. The unusually large proportion (39%) of patients with non-A non-B acute pancreatitis might have resulted from the fact that our unit is a referral center for regional institutions. Furthermore, certain data, e.g. CRP level or laboratory results needed to calculate the Ranson score, were missing in certain patient files. We used the Balthazar score described in 1985 [11] instead of the amended score described in 1990 [12] to facilitate a more accurate retrospective analysis, particularly because a CT-scan was not always performed under standard conditions. Referral practices may have increased the number of patients with severe clinical presentations, notably necrotizing pancreatitis. Inversely, exclusion of patients without a CT-scan or who had not been hospitalized might have lowered the number of patients with benign pancreatitis.

Other authors have tried to determine whether the severity of acute pancreatitis is cause-dependent. Various conclusions drawn from both retrospective and prospective studies are often discordant. For example some authors have found alcoholic acute pancreatitis to be more severe than other forms [17-19]; such a difference has not been confirmed by others [20, 21]. Several reasons would explain this discordance: different ways of defining acute pancreatitis, small number of patients with non-A non-B acute pancreatitis, different methods for analyzing severity (mortality, morbidity, criteria predictive of severity), and finally different ways of determining patient classification (detailed descriptions of exploration methods used to search for the cause of acute pancreatitis are not always presented).

The goal of these earlier studies was to search for a difference in the distribution of causes of acute pancreatitis as a function of the presence or absence of criteria of severity in order to identify a group of patients with acute pancreatitis who could benefit from an etiological work-up. This is an everyday problem but no satisfactory solution has been found. In our work, standardized complementary examinations and a multidisciplinary evaluation of the patient files enabled a precise diagnosis of etiology and severity. The standardized exhaustive etiological work-up limited the number of patients with acute pancreatitis of undetermined origin (9% versus 20-25% in the literature) [25].

In our population the proportion of patients with non-A non-B acute pancreatitis was lower in the subgroup with a Balthazar score = D (27%) than in the subgroup with non-necrotizing acute pancreatitis. The distribution of causes was the same for all of the other severity criteria (whether these were a priori or a posteriori factors). This finding demonstrates that an equally exhaustive search for non-A non-B causes of acute pancreatitis must be carried out in patients with severe disease (15% to 50% of the patients in our recruitment) irrespective of the set of criteria used to define severity. This search often discloses a curable cause of acute pancreatitis, allowing proper management and preventive measures.

In conclusion, while the proportion of non-A non-B causes of acute pancreatitis is lower in patients with necrotizing pancreatitis (Balthazar score = D), such causes can be identified in more than one quarter of these patients (27% in our experience). No difference in etiology was found for other criteria of severity, but non-A non-B was found in 15 to 50% of the patients with severe acute pancreatitis, warranting an exhaustive etiological work-up in search of an identifiable origin, particularly obstruction.

### REFERENCES


