Incidence and severity of non alcoholic and non biliary pancreatitis in a gastroenterology department

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SUMMARY

Aims — Etiological investigations proposed for patients with acute pancreatitis have been evolving considerably these past few years, significantly limiting the number of cases labeled idiopathic. The aim of this study was to determine the incidence of non alcoholic non biliary pancreatitis and identify causes, comparing severity by etiology.

Patient and methods — This retrospective analysis included 108 patients managed from October 1996 to April 2005. Standardized extensive etiological investigations were performed. The following criteria of severity were recorded: peak CRP value, Ranson score, Balthazar score, duration of hospital stay and pseudocyst occurrence.

Results — The cause of acute pancreatitis was alcohol (N= 45), gallstones (N=50), obstruction (N=10), unknown (N=10), drugs (N=9), auto-immunity (N=4), infections (N=3), post-operative (N=2), post-ERCP (N=2), trauma (N=1), hypertriglyceridemia (N=1), genetic (N=1). The main criteria of severity were significantly different between non alcoholic non biliary pancreatitis and the other causes (CRP>120 mg/L, Ranson score >3 and Balthazar score ≥D) while other criteria (pseudocyst occurrence and duration of hospitalisation) were similar. Mean peak CRP was 79.5 mg/L for the overall population and varied significantly by etiology: peak CRP for drug-induced acute pancreatitis (4.6 mg/L) was significantly lower than for the other causes (P<10^-6).

Conclusion — This study shows that non alcoholic non biliary causes account for one third of the cases of acute pancreatitis, usually with a mild to moderate presentation. As the mean peak CRP value is significantly lower in drug-induced acute pancreatitis, careful search for an adverse drug reaction is appropriate in patients with acute pancreatitis of unknown cause and a low peak CRP level.

RÉSUMÉ

Incidence et sévérité des pancréatites non alcooliques et non biliaires dans un service d’hépato-gastroentérologie

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Introduction — La recherche des étiologies des pancréatites aiguës (PA) non alcooliques (A) non biliaires (B) a évolué ces dernières années avec un recul important de la proportion des pancréatites dites idiopathiques. Le but de cette étude rétrospective était de définir la proportion de pancréatites aiguës non A non B ainsi que leurs étiologies en nous attachant à comparer la sévérité de ces pancréatites selon leur étiologie.

Malades et méthodes — D’octobre 1996 à avril 2005, 138 malades ont été inclus dans l’étude. Ils avaient un bilan standardisé et exhaustif à la recherche des causes potentielles. Les critères de sévérité suivants étaient étudiés rétrospectivement : pic de protéine C-reactive, score de Ranson, score de Balthazar, durée d’hospitalisation, survenue d’un pseudo-kyste.

Résultats — La cause de PA était alcoolique (N = 45), biliaire (N = 50), obstructive (N = 10), indéterminée (N = 10), médicamenteuse (N = 9), auto-immune (N = 4), infectieuse ou parasitaire (N = 3), postchirurgicale (N = 2), traumatique (N = 1), hypertriglycéridémique (N = 1), génétique (N = 1). Les PA non A non B étaient significativement moins fréquentes parmi les PA ayant un pic de CRP > 120 mg/L, un score de Ranson > 3 et un score de Balthazar ≥ D. Le pic moyen de CRP était de 79,5 mg/L et différait de façon significative selon l’étiologie avec une CRP moyenne de 4,6 mg/L pour les PA médicamenteuses, significativement plus basse que pour les autres étiologies (P < 10^-6).

Conclusion — Cette étude montre que les pancréatites aiguës non alcooliques non biliaires représentent près d’un tiers des pancréatites aiguës et sont moins fréquentes dans le groupe des pancréatites sévères. Le pic moyen de CRP était significativement plus bas dans les pancréatites aiguës médicamenteuses. Ce résultat incite à rechercher une origine médicamenteuse chez tout patient présentant une pancréatite aiguë avec un pic de CRP bas et sans autre étiologie évidente.
Introduction

The incidence of acute pancreatitis (AP) ranges from 5 to 50 cases per 100,000 inhabitants, on steady rise since the eighties [1]. The two main causes, biliary disease and alcohol abuse, account for about 80% of cases, non-alcohol non-biliary (non-A non-B) AP being relatively less frequent [1, 2].

Among patients with non-A non-B AP, the proportion with idiopathic disease has also declined because of advances in morphology investigations and a more detailed search for autoimmune, drug-induced, or genetic causes. Non-A non-B AP may however be severe, some suggesting it may be the cause of one quarter of all cases of necrotizing pancreatitis [3].

The purpose of this retrospective analysis was to determine the incidence and causes of non-A non-B AP among patients hospitalized in a hepatogastroenterology unit and to ascertain disease severity in comparison with alcoholic or biliary AP. Our unselected recruitment population includes all causes of AP, providing an opportunity to avoid recruitment bias.

Material and methods

Patients

This was a retrospective study which included all adult patients hospitalized in the Bégin Army Instruction Hospital from October 1996 through April 2005 for management of AP. Patients were referred to the hepatogastroenterology unit directly from the hospital emergency admissions room.

Inclusion criteria

Patients presenting an acute episode of AP were included. AP was defined as pain compatible with pancreatic disease associated with: a) elevated serum lipase and/or serum amylase ≥3 x upper limit of normal, or b) elevated serum lipase and/or plasma amylase ≥ 2 x upper limit of normal and imaging proof of pancreatic inflammation [4].

Exclusion criteria

Patients whose medical files were insufficient to determine the severity or cause of AP were excluded from the analysis.

Methods

Variables studied

Data were collected from the archives of the intensive care and hepatogastroenterology unit of the Bégin hospital. The following data were extracted from patient files: age, gender, total duration of hospital stay, cause of AP, peak C-reactive protein (CRP) within 72 hr of admission, Ranson score, and Balthazar score on the abdominal computed tomography (CT) performed within 72 hr of admission. The Ranson score >3 [5], peak CRP>120 mg/L [6], and presence of local or regional complications according to the Atlanta classification [7] were used to define disease severity. Necrosis was defined by Balthazar score ≥8 [8], pseudocyst ≥ 2 cm, sepsis-related organ failure determined by the sepsis-related organ failure assessment (SOFA) score [9], presence of at least one episode of generalized sepsis, requirement for emergency surgery for the treatment of complications of AP, and AP-related death.

Abbreviations:

AP = Acute pancreatitis
Non A = Non alcoholic
Non B = Non biliary
CRP = C-reactive protein
CDT = Carboxy deficient transferrin
ERCP = Endoscopic retrograde cholangiopancreatography

Causes of AP

The following criteria were used to identify for causes of AP: — alcoholic AP was defined as alcohol use during the days before admission, confirmed by history taking and serum carboxy deficient transferrin (CDT)≥2.6%, with no evidence favoring a biliary cause or another cause; — biliary AP was defined as the presence of a gallstone proven by ultrasound (US) or CT, micturition or sludge in the bladder or common duct proven by endoscopic US performed after interruption of fast, with no evidence of chronic alcohol abuse or signs favoring another cause.

Search for causes of non-A non-B AP:

— obvious cause because of the medical history (trauma, operation, endoscopic retrograde cholangiopancreatography (ERCP)), laboratory results (elevated serum triglycerides or calcium), or morphological findings (tumor or anatomic obstruction);

— if no obvious cause could be identified, a secondary extensive work-up was undertaken to search for an infection (HBV, HAV, HIV 1 and 2, coxackie virus B1-B6, echovirus, infectious mononucleosis, Epstein Barr virus, measles, herpes zoster, yersinia, brucella, legionella, mycoplasma pneumoniae, salmonella, cytomegalovirus, chlamydiae trachomatis and pneumoniae), a genetic cause (search for cationic trypsinogen mutations and mutations of the cystic fibrosis CFTR protein gene), an autoimmune cause (rheumatoid factor, anti-nuclear antibodies) and drug reactions using standard criteria for attribution of cause [10, 11]; — the cause of AP was considered undetermined when all of the preceding causes were ruled out [12].

Statistical analysis

Pearson’s chi-square test, Fisher’s exact test and the Kruskal-Wallis test were applied as appropriate. P<0.05 was considered significant. Results are reported as mean ± standard deviation or absolute value (percentage).

Results

General characteristics

The series retained for analysis 138 patients (64.5%) among 142 files retained for examination. The causes of AP were: alcohol (N=45), biliary disease (N=50), obstruction (N=10) [cholangiocarcinoma (N=3), adenocarcinoma of the pancreas (N=2), intraductal papillary mucinous tumors of the pancreas (IPMN) (N=2), sphincter of Oddi dysfunction (N=1)], pancreas divisum (N=1), choledococele (N=1), undetermined (N=10), drug-induced (N=9), auto-immune disease (N=4) [Crohn’s disease (N=3), lupus (N=1)], infection or parasite (N=3) [malaria (N=1), Yersinia (N=1), Mycoplasma pneumoniae (N=1)], post-operative (N=2), post-ERCP (N=2), post-traumatic (N=1), hypertriglyceridemia (N=1), genetic (N=1).

Non-A non-B AP was noted in 29.1% of the study population. Duration of hospital stay was 14.4±2.4 days and was similar for the different causes. Age and gender varied with cause (table I). In patients aged less than 50 years, alcoholic AP was significantly more frequent (56%) than biliary AP (13%) or non-A non-B AP (31%) (P<10^-6). After the age of 50 years, biliary AP predominated (57%) over alcoholic (17%) and non-A non-B AP (26%) (P<10^-6). Biliary AP (52%) was significantly more frequent among women than alcoholic AP (10%) or non-B non-A AP (38%) (P<10^-6). Alcoholic AP was significantly more frequent among men (45%) than biliary AP (28%) or non-A non-B AP (27%) (P<10^-6). There was no significant difference by gender for the other causes.

Disease severity

Peak CRP, Ranson and Balthazar score were available for all patients. CRP was ≥120 mg/L in 46 patients (33.6%). The mean CRP was 79.5±12.9 mg/L and varied significantly with cause of
AP; peak CRP was lower among patients with drug-induced AP (p<10^-5) (Table II). The Ranson score at admission was ≥3 in 16 patients (11.6%) and the Balthazar score was ≥D in 46 (33.6%). Among these 46 patients, peak CRP was <120 mg/L in 25 and the Ranson score <3 in 33. Seventeen patients (12.3%) required intensive care at admission. Mean duration of stay in the intensive care unit was 15.5±12.4 days. Complications noted during the course of the acute episode of AP were, by order of frequency: pseudocyst measuring ≥2 cm (N=16 patients, 11.8%), infection (N=6, 4.4%), multiple organ failure (N=5, 3.6%), death (N=4, 2.9%, 3 patients with alcoholic AP and 1 patient with biliary AP).

Severity of non-A non-B AP

Non-A non-B pancreatitis was encountered in 5 of 46 (10.8%) cases of AP with CRP≥120 mg/L and in 38 of 92 (41.3%) with CRP<120 mg/L (P=0.001). Non-A non-B AP was observed in 1 of 16 cases (6.3%) of AP with a Ranson score ≥3 and 42 of 122 (34.4%) with a Ranson score <3 (P=0.01). Non-A non-B AP occurred in 8 of 46 (17.4%) cases of AP with a Balthazar score ≥D and in 35 of 92 (38%) with a Balthazar score <D (P=0.002). Non-A non-B AP was observed in 2 of 16 (12.6%) cases of AP complicated by a pseudocyst and in 41 of 122 without a pseudocyst (NS). Mean duration of hospital stay was not affected by cause of AP and similarly admission to the intensive care unit had no effect on length of hospitalization. No significant difference was noted for the other variables examined.

Discussion

Our study was designed after the study conducted in the Beaujon hospital in 2003 [3]. Unlike the Beaujon gastroenterology unit which is a university referral center, our unit has the direct recruitment of a general hospital. We thus avoided recruitment bias which can lead to an overestimation of the incidence of severe AP and non-A non-B AP [3]. Nevertheless, the present series was retrospective and recruited in a single center. In addition, for the Balthazar score, we used the 1985 classification [13], which is more readily and more accurately determined from retrospective data [3] than the 1990 classification [8].

Biliary disease and alcohol abuse are the leading causes of AP, reported in 55-85% of patients in reports in the literature [3, 14-21]. In France, reported incidence of biliary AP has ranged from 24% to 46% whereas the figures for alcoholic AP have exhibited less variability (33-38%) [3, 18-21]. Nevertheless, gallstones appear to be the leading cause of AP, reported for 38-43% of patients, whereas alcoholic AP has been found in 31% of patients [1, 22]. The proportions were similar in our series where the incidence of biliary AP was slightly higher than that of alcoholic AP (36% versus 33%).

The incidence of alcoholic AP was significantly higher among patients aged less than 50 years, biliary AP predominating among their older counterparts. This is in agreement with Blamey et al. [22] who studied 405 patients and Barkun et al. [23] who reported that among 106 patients, age was a predictive factor with a cutoff at about 50-55 years. We found a significantly higher incidence of alcoholic AP among men and a significantly higher incidence of biliary AP among women. Blamey also reported that female gender was an independent predictive factor, but linked with age at multivariate analysis [22]. Epidemiological data confirms the female predominance of a biliary cause, biliary AP being twice as frequent in women as in men [1].

The incidence of non-A non-B AP was 31% in our series. This is similar to figures reported in the literature where estimates have been around 30%, ranging from 15-39% [3, 14-21]. Estimates for diverse causes and idiopathic AP (retrospectively 24% and 7% in our study) have been quite variable in the literature: 3.6% to 29.2% for diverse causes and 6.6% to 21% for idiopathic AP [3, 14-21]. The incidence of idiopathic AP appears to be lower in studies where the incidence of diverse causes is higher. The contrary is also true, a high incidence of idiopathic AP being noted in studies where the incidence of diverse causes

| Table I. – Age and gender according to etiology of acute pancreatitis.  
| Distribution de l’âge et du sexe pour chaque étiologie.  |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Alcohol disease | Biliary disease | Diverse disease | Undetermined disease | Drug-induced | Obstruction | Post-ERCP |
| Mean age. years | 40.9 | 66.4 | 41.3 | 52.7 | 36.1 | 55.0 | 51.5 |
| [Standard deviation] | [10.8] | [17.2] | [19.6] | [24.1] | [18.3] | [20.3] | [2.1] |
| Males N | 40 | 25 | 8 | 5 | 4 | 6 | 1 |
| (%) | (88.9) | (50.0) | (66.7) | (50.0) | (44.4) | (60.0) | (50.0) |

The differences are significant for age (P<0.00001) and gender (P<0.00001).

| Table II. – Peak C-reactive protein level by etiology.  
| Distribution du pic de CRP en fonction de l’étiologie.  |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Alcohol disease | Biliary disease | Diverse disease | Undetermined disease | Drug-induced | Obstruction | Post-ERCP |
| CRP | 87.1 | 99.9 | 71.1 | 70.1 | 28.5 | 4.6 | 87.5 |
| median | 92.0 | 72.5 | 25.4 | 59.1 | 25.5 | 3.9 | 87.5 |
| SD | 68.3 | 96.3 | 103.3 | 56.6 | 25.6 | 2.9 | 46.0 |
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is low. This can be explained by the fact that for some patients, the diagnosis of a diverse cause is established for acute episodes which earlier would have been considered a manifestation of idiopathic AP. This highlights the importance of using, as in the present study, a standardized diagnostic protocol to search for an autoimmune, a drug-induced or a genetic cause of AP.

There is little agreement in the literature concerning the severity of non-A non-B AP. The fact that most studies only report a small number of cases and have not used a standardized management protocol is a probable explanation for this lack of consensus. Classically, non-A non-B AP is considered a generally benign though recurrent disease [24], Hentic et al. [3] had a lower proportion of patients with a Balthazar score $\geq D$ among their cases of non-A non-B AP which nevertheless accounted for more than one quarter of the cases of necrotizing AP. More than 35% of their non-A non-B cases were complicated by pseudocysts. In our series, the proportion of non-A non-B cases was significantly lower in patients with CRP $\geq 120$ mg/L, a Ranson score $\geq 3$ and a Balthazar score $\geq D$. We were unable to identify any significant difference for the other variables studied. These findings suggest that non-A non-B AP is a moderately severe disease which in most patients follows a benign course.

The incidence of drug-induced AP among the cases of non-A non-B AP was 7% in our series. This is a higher percentage than reported in the literature (0-2%). This higher rate of drug-induced AP must be examined with precaution due to the difficulty in attributing causality. Peak CRP was significantly lower in cases of drug-induced AP ($<5$mg/L) [P<10⁻⁶], while the Ranson score was <3 and the Balthazar score <D in nine patients. These cases all followed a benign course. The small sample size hinders interpretation of this finding, but the outcome of drug-induced AP is not always favorable; fatal cases have been reported [25]. Nevertheless, the fact that disease course is usually favorable in patients with drug-induced AP, as demonstrated by Lankish in 1995 [26], suggests that the real incidence is probably underestimated. The zero incidence of drug-induced AP in certain reports with a large number of cases [24] would be in favor of this hypothesis.

In conclusion, non-A non-B acute pancreatitis accounts for about one-third of all cases of acute pancreatitis and is significantly less frequent among patients with peak CRP $\geq 120$ mg/L, a Ranson score $\geq 3$, and a Balthazar score $\geq D$. A rigorous etiological search is nevertheless required since the identification of a curable cause would allow implementation of measures to prevent recurrent episodes. The use of a standardized etiological diagnostic work-up would limit the proportion of cases of AP with an undetermined cause. In our series, this approach enabled the identification of a higher percentage of drug-induced AP (7% versus 2% reported in the literature) significantly associated with lower peak CRP than other cases of AP. This finding suggests that the search for an adverse drug reaction should be undertaken in all patients presenting a mild episode of acute pancreatitis with a low CRP level and no obvious cause.

REFERENCES