

Acute pancreatitis in children. An Italian multicentre study

R. Pezzilli
A.M. Morselli-Labate¹
E. Castellano⁵
C. Barbera⁶
S. Corrao³
L. Di Prima²
V. Lucidi⁴
A. Carroccio²

Aim. To evaluate the clinical, morphological and aetiological aspects of acute pancreatitis in children in Italy.

Patients. The hospital records of 50 consecutive patients with acute pancreatitis observed in 5 Italian Pediatric Departments were reviewed.

Results. A total of 25 males and 25 females (median age 10.5 years, range 2-17) were studied. Of these patients, 48 (96%) had abdominal pain. The pancreatitis was associated with biliary disease in 10 patients (20%); it was due to viral infection in 6 patients (12%), pancreatic duct abnormalities in 4 (8%), familial chronic pancreatitis in 3 (6%), trauma in 5 (10%) and other causes in 5 (10%); the pancreatitis was of unknown origin in 17 patients (34%). Previous attacks of the disease had occurred in 14 patients. A diagnosis of mild pancreatitis was made in 41 patients (82%) and of severe disease in 9 (18%). One patient with severe pancreatitis died from multiorgan failure. Patients with severe pancreatitis had significantly higher serum concentrations of C-reactive protein than patients with mild pancreatitis. Hospital stay was similar for patients with the mild form and those with the severe form of the disease.

Conclusions. In Italian children, acute pancreatitis is of unknown origin in about one-third of the children and is recurrent in 28% of the cases. The disease is severe in 18% of the cases.

Digest Liver Dis 2002;34:343-8

Key words: acute pancreatitis

Introduction

Acute pancreatitis is a relatively unusual disease in children and the diagnosis is often delayed¹. There are only a few reports in the literature which refer to large series of patients²⁻⁷. In particular, data regarding acute pancreatitis in Italian children are limited⁸ and, for these reasons, we reviewed all cases of acute pancreatitis occurring in 5 large Italian Pediatric Departments over a two-year period (1998-1999). Aim of the investigation was to provide data about the clinical, morphological and aetiological aspects of acute pancreatitis in children in our country.

Patients and Methods

All cases with primary code 577.0 (acute pancreatitis) according to the ICD-9-CM in 5 Italian Paediatric Departments between January 1998 and December 1999 were retrospectively examined. Cases of recurrent pancreatitis (code 577.1) and unspecified pancreatitis (code 577.9) were not retrieved and cases with codes, 577.2 (cysts and pseudocysts of the pancreas), and 577.8 (other specified diseases of the pancreas) were also excluded. The Centres taking part in the investigation are all mixed medical/surgical departments (four universities and one general hospital) representative of

From

Department of Internal Medicine and
¹ Department of Internal Medicine and
Gastroenterology, "Sant'Orsola" Hospital
and University of Bologna, Bologna;
² University Hospital, ³ "Di Cristina" Hospital,
Palermo; ⁴ "Bambin Gesù" Hospital, Rome;
⁵ "Gaslini" Hospital, Genoa; ⁶ University
Hospital, Turin, Italy.

Address for correspondence

Dr. R. Pezzilli, Dipartimento di Medicina
Interna, Ospedale "Sant'Orsola", via
Massarenti 9, 40138 Bologna, Italy.
Fax: +39-051-549653.
E-mail: pezzilli@orsola-malpighi.med.unibo.it

Submitted July 27, 2001.

Accepted after revision December 23, 2001.

the entire country: Northern Italy (Paediatric Departments of the University Hospital of Turin, "Gaslini" Hospital of Genoa, "Sant'Orsola" Hospital of Bologna), Central Italy ("Bambin Gesù" Hospital of Rome) and Southern Italy ("Di Cristina" Hospital of Palermo). The hospital records of all patients discharged with the diagnosis of acute pancreatitis were reviewed by one reviewer per site and were included in the study. Possible discrepancies were resolved by discussion between the local reviewer and the coordinator of the study.

Each patient's medical record was evaluated to determine presence and duration of pain, aetiology of the disease, clinical course, complications and the outcome of the disease. Furthermore, the results of the following radiological investigations, when performed, were included: chest X-rays, plain film abdominal X-rays, abdominal ultrasonography. Abdominal contrast-enhanced computed tomography was carried-out when no visualisation of the pancreas was found at ultrasonography or to better define the extent of pancreatic necrosis; endoscopic retrograde cholangiopancreatography was performed when a biliary disease was suspected. The behaviour of serum amylase, lipase and C-reactive protein (CRP) and other biochemical parameters (erythrocyte sedimentation rate, white blood cell count, haemoglobin, haematocrit, blood glucose, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl-transpeptidase, alkaline phosphatase, albumin, blood urea nitrogen (BUN), creatinine, calcium, sodium, and potassium) were also evaluated, when present in the medical records, for the first three days after admission. The reference values of the erythrocyte sedimentation rate, white blood cell count, haemoglobin, haematocrit, blood glucose, total bilirubin, albumin, BUN, creatinine, calcium, sodium, and potassium were the same in all the five centres. The reference values of amylase, lipase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl-transpeptidase, and alkaline phosphatase varied in the five centres, therefore, the values were calculated and reported as multiples of the upper reference limit (URL).

A diagnosis of idiopathic pancreatitis was considered when identifiable causes of acute pancreatitis had been excluded.

No genetic investigations were done in patients with suspected hereditary pancreatitis.

Statistical analysis

The Wilcoxon matched-pairs test was used for the within-subject comparison of continuous variables between the different time periods. The Mann-Whitney and the Yates' corrected chi-squared tests⁸ were used to

compare continuous and nominal variables, respectively, between different groups of patients. Statistical analyses were performed by running the SPSS/PC+ statistical package⁹ on a personal computer. Two-tailed *p* values less than 0.05 were considered statistically significant.

Results

A total of 50 cases of acute pancreatitis were found, according to the discharge code (ICD-9-CM 577.0). There were 25 males and 25 females; median age was 10.5 years (range 2-17). Of the 50 patients, 48 (96%) had abdominal pain; the median duration of pain was 5 days (range 0-59). One of the two patients without abdominal pain had abdominal trauma and the other had pancreatitis of unknown origin. However, in these two patients, the results of biochemical and imaging examinations were compatible with acute pancreatic inflammation as they presented serum amylase and lipase increase and enlargement of the pancreas with oedema. Serum amylase and lipase concentrations were recorded in all patients upon admission and for the following two days (Fig. 1). The serum pancreatic enzyme concentrations progressively and significantly decreased from the 1st to the 3rd day of hospitalization.

Table I shows the values of the other biochemical parameters evaluated during the first three days of hospitalization.

As far as concerns radiological examinations, abdominal ultrasonography was performed in all patients, whereas contrast-enhanced computed tomography was

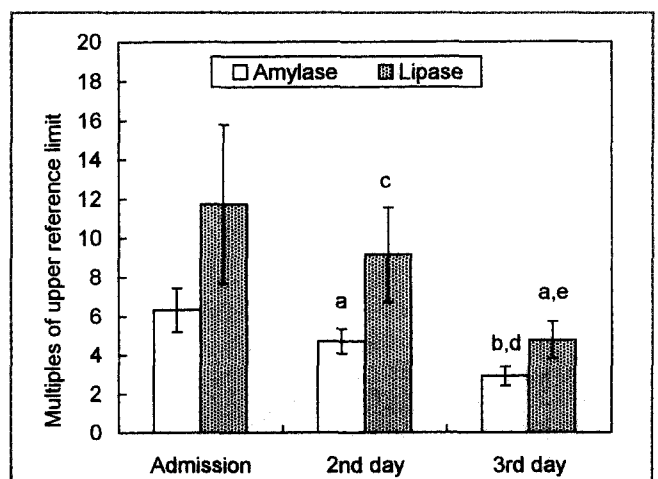


Fig. 1. Behaviour of serum amylase and lipase during first three days of hospitalization. Results expressed as multiples of upper reference limit and are reported as mean ± SEM. ^a *p* < 0.01; ^b *p* < 0.001; ^c *p* < 0.05 vs admission; ^d *p* < 0.001; ^e *p* < 0.01 vs 2nd day.

Table I. Biochemical parameters in patients with acute pancreatitis.

	Admission	2 nd day	3 rd day
Erythrocyte sedimentation rate (1 st hour; mm/h)	21.3±12.6 (24)	20.8±17.4 (4)	27.7±17.3 (6)
White blood cell count (μl ⁻¹)	9,704±4,331 (46)	7,937±4,185 ^a (22)	7,294±3,229 ^b (21)
Haemoglobin (g/dl)	13.2±1.4 (46)	12.5±1.0 (20)	12.2±1.4 ^c (20)
Haematocrit (%)	39.2±4.3 (45)	37.7±3.0 (21)	36.9±4.3 (21)
Blood glucose (mg/dl)	104.0±46.0 (45)	111.3±27.0 (22)	119.0±70.0 (25)
Total bilirubin (mg/dl)	1.1±1.1 (29)	2.4±2.3 (10)	1.4±1.2 (15)
Aspartate aminotransferase (multiple URL)	1.3±1.7 (45)	1.6±1.9 (26)	1.1±1.0 (24)
Alanine aminotransferase (multiple URL)	1.4±3.0 (44)	2.3±4.0 (25)	1.4±2.2 (25)
Lactate dehydrogenase (multiple URL)	1.1±0.4 (17)	1.3±0.3 (4)	1.1±0.3 (4)
Gamma-glutamyl-transpeptidase (multiple URL)	3.7±11.6 (28)	3.4±3.8 (12)	3.0±3.3 (12)
Alkaline phosphatase (multiple URL)	1.3±0.8 (24)	1.2±0.6 (8)	1.4±0.7 (5)
Albumin (g/dl)	4.8±1.7 (22)	3.8±0.6 (4)	4.0±1.0 (6)
BUN (mg/dl)	20.2±11.0 (34)	20.0±7.5 (13)	19.6±7.6 (13)
Creatinine (mg/dl)	0.7±0.21 (36)	0.7±0.3 (14)	0.6±0.2 (16)
Calcium (mg/dl)	9.3±0.7 (41)	9.4±0.7 (15)	9.4±0.5 (21)
Sodium (mEq/l)	137.8±4.0 (44)	136.6±3.6 (20)	136.8±2.8 (25)
Potassium (mEq/l)	4.2±0.5 (43)	4.4±0.6 (21)	4.4±1.0 (23)

Results are reported as mean ± SD. Number of observations are indicated in parentheses; ^a p=0.001; ^b 0.010; ^c 0.026 vs. admission. Abbreviations: see list.

performed in only 17 patients (34%) in a median time of 6 days (range 1-30) from hospital admission. Of the 50 patients, 14 (28%) also underwent diagnostic endoscopic retrograde cholangiopancreatography examinations in a median time of 12.5 days (range 0-60) from admission. Fifteen patients (30%) underwent plain abdominal X-ray which demonstrated a sentinel loop in 3 patients, and 21 patients (42%) underwent chest X-rays which demonstrated pleural effusion in 1 child and pulmonary densifications in two.

The aetiology of acute pancreatitis is shown in Table II. The pancreatitis was associated with biliary disease in 10 patients (20%) and was due to viral infection in

6 (12%), pancreatic duct abnormalities in 4 (8%), familial chronic pancreatitis in 3 (6%), trauma in 5 (10%) and other causes (Type IV hyperlipidaemia, duodenal duplication, azathioprine for the treatment of psoriasis, cystic fibrosis and coeliac disease) in 5 (10%). The pancreatitis was of unknown origin in 17 patients (34%). No significant differences in sex (p=1.000) and age (p=0.394) were found between subjects with acute pancreatitis of known and unknown origin.

Of the 50 patients, 14 (28%) had had previous attacks of acute pancreatitis (Table II). The number of previous attacks of acute pancreatitis was: 6 in one patient

Table II. Aetiology of acute pancreatitis in 50 children studied. Number of patients with previous attacks of acute pancreatitis (AP) and those with severe form of disease are also reported.

	No. cases	Previous AP	Severe AP
Idiopathic	17 (34%)	6	4
Biliary diseases	10 (20%)	2	-
Biliary lithiasis	6	-	-
Biliary malformation	4	2	-
Viral infections	6 (12%)	1	2
Mumps	4	-	1
Rotavirus	1	-	-
HIV	1	1	1
Trauma	5 (10%)	-	2
Pancreatic duct abnormalities	4 (8%)	2	-
Familial chronic pancreatitis	3 (6%)	2	-
Cystic fibrosis	1 (2%)	-	-
Type IV hyperlipidaemia	1 (2%)	1	1
Duodenal duplication	1 (2%)	-	-
Coeliac disease	1 (2%)	-	-
Drugs (Azathioprine)	1 (2%)	-	-

with biliary disease, 5 in two patients (1 with biliary disease and 1 with the idiopathic form of the disease) and 3 in three patients [2 with idiopathic acute pancreatitis and 1 with human immunodeficiency virus (HIV) infection].

On the basis of the Atlanta criteria¹¹, 41 patients (82%) were diagnosed as having mild acute pancreatitis and 9 (18%) as having the severe form of the disease. The aetiology of the 9 patients with severe acute pancreatitis was: idiopathic in 4, viral in 2, trauma in 2 and Type IV hyperlipidaemia in 1. Systemic and local complications were as follows: pulmonary in 4, renal in 2, metabolic alterations in 3, cardiovascular in 1, pancreatic pseudocysts in 2 and one patient with infected pancreatic necrosis died. Therefore, the mortality rate accounted for 2% in the general population and for 11% in patients with severe acute pancreatitis. The duration of pain was not significantly different ($p=0.720$) between patients with severe pancreatitis (8.7 ± 8.7 ; mean \pm SD) and those with the mild form (12.1 ± 18.1 ; mean \pm SD).

Serum CRP determination was carried out in 22 patients on admission to the hospital, in 4 on the 2nd day of hospitalization and in 12 patients on the 3rd day; data related to the second day of hospitalization were not included in the statistical analysis. Patients with severe pancreatitis had significantly higher serum CRP concentrations than patients with mild acute pancreatitis on the day of admission ($p=0.008$) and on the 3rd day of hospitalization ($p=0.033$) (Fig. 2). Regarding the other biochemical parameters, serum calcium concentrations, on the second day after admission, were significantly lower ($p=0.020$) in patients with severe acute pancreatitis (8.43 ± 0.56) than in those with the mild form of the disease (9.58 ± 0.55). Serum potassium con-

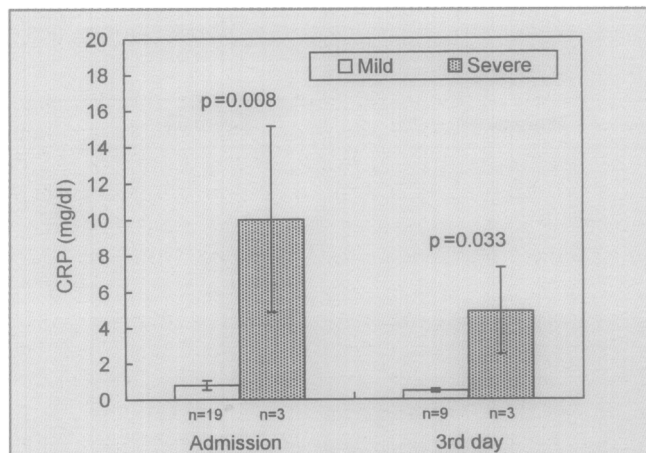


Fig. 2. Behaviour of serum C-reactive protein (CRP) on day of admission and on 3rd day of hospitalization. Results reported as mean \pm SEM.

centrations were significantly higher ($p=0.034$) in patients with severe acute pancreatitis (4.87 ± 0.79) than in those with mild acute pancreatitis (4.17 ± 0.29) on the second day of illness. The haematocrit value was significantly lower ($p=0.008$) in children with severe acute pancreatitis (29.3 ± 5.0) than in those with the mild form (38.1 ± 2.7) only on the third day after admission.

As reported in Table III, 7 of the 50 patients (14%) underwent surgery, which was elective in 5. Surgery was performed in one (11.1%) of the 9 patients with severe acute pancreatitis and in 6 (14.6%) of the 41 patients with the mild form ($p=1.000$). The median time elapsing between admission and surgery was 47 days (range 10-365).

The median hospital stay was 13 days (range 4-46) in patients with mild acute pancreatitis and 20 days (range 6-51) in those with the severe form ($p=0.326$).

Discussion

Results as reported of the first multicentre study on childhood acute pancreatitis performed in Italy. Although it was a retrospective study, exclusively based on clinical, laboratory and imaging data derived from the clinical records, these data are, in our opinion, valuable as they permit paediatricians to see the clinical approach to an uncommon disease and, moreover, provide the opportunity of identifying unsolved issues which merit investigation by means of further prospective studies. Furthermore, it should be emphasized that relatively few studies have focused on acute pancreatitis in children²⁻⁷ and, in this respect, the picture of this disease, in our country, can help to clarify some clinical and aetiological aspects.

We found an equal distribution of sex in children with acute pancreatitis; this finding is similar to that reported in adults¹²⁻¹⁴. The median age at onset of the disease was 10.5 years and no cases of acute pancreatitis were observed in infants under the age of two years, al-

Table III. Type and indication of surgery in 7 patients with acute pancreatitis.

	No. patients	Indication
Laparotomy in emergency	2 ^a	Diagnostic
Choledochojejunostomy	1	Biliary abnormality
Pancreatic head resection	1	Pseudocyst
Cystojejunostomy	1	Pseudocyst
Sphincterotomy	2	Biliary lithiasis
Total	7	

^a 1 patient with severe acute pancreatitis due to abdominal trauma.

though, in some patients congenital malformations of the biliary tree and the pancreatic duct were reported. As regards clinical presentation, the results of our study also confirm that, in children, as in adults¹⁴, abdominal pain is the symptom of presentation in the vast majority of patients with acute pancreatitis; only two patients did not experience abdominal pain: 1 with acute pancreatitis due to abdominal trauma and 1 with acute pancreatitis of unknown origin. The median duration of the pain was 5 days and there was no significant relationship with the severity of acute pancreatitis. Concerning the aetiology of the disease, we found that the most common cause of acute pancreatitis in the paediatric population is still unknown (34%), whereas biliary disease – which is the main aetiological factor of acute pancreatitis in Italian adults¹²⁻¹⁴ – is less frequent (20%). In this respect, the data emerging from the present study are similar to those reported by Mader and McHugh¹⁵ in a review of 304 paediatric patients with acute pancreatitis. Regarding viral infection as a cause of acute pancreatitis, we found that mumps is the predominant virus involved, whereas rotavirus infection and HIV may also cause acute pancreatitis but in a smaller percentage of cases. Indeed, only two previous papers have reported rotavirus infection as a cause of acute pancreatitis^{16 17}. The only patient with acute pancreatitis and HIV infection had the severe form of the disease. Unfortunately, no genetic investigations were carried out in the 3 patients with familial chronic pancreatitis; thus, the hereditary form of pancreatitis in these patients may be only hypothesized.

As in the study of Weizman and Durie⁷, about one-third of the patients in our investigation, experienced one or more recurrences of acute pancreatitis and 6 of these 14 patients had idiopathic acute pancreatitis suggesting that one of the most interesting aspects of acute pancreatitis in children is the large percentage of cases which remain of unknown aetiology. This point must be better clarified by further studies which should include regular screening for cystic fibrosis, coeliac disease, hereditary pancreatitis and other familial conditions which predispose to acute pancreatitis.

Regarding the diagnostic biochemical evaluation, the behaviour of amylase and lipase, the most common serum assays employed for the diagnosis of acute pancreatitis, was similar to that found in the adult population¹⁸.

Apart from ultrasonography which was carried out in all patients, imaging techniques, such as abdominal X-rays, chest X-rays and contrast-enhanced computed tomography, were performed in less than 40% of the patients recruited. On the other hand, endoscopic retrograde cholangiopancreatography was carried out in 28% of the children and was used for diagnostic purposes in all of them. This finding is quite surprising,

since endoscopic retrograde cholangiopancreatography should be performed only if a therapeutic option exists; in fact, magnetic resonance cholangiopancreatography is a safer technique for diagnosing pancreatic diseases¹⁹. Furthermore, the data in our study showed that the frequency of severe acute pancreatitis is quite similar to that found in adults¹²⁻¹⁴.

In recent years, multiple score systems, as well as single markers, have been used in clinical practice to establish the severity of acute pancreatitis in adults²⁰. Despite this, it seems that clinicians caring for children with acute pancreatitis do not generally perform investigations shown to be of significance in detecting severe disease. In fact, in our study, CRP, which is a well-known index of the severity of acute pancreatitis²⁰, was performed in less than 50% of the children studied. CRP determination, when performed, was able to distinguish the mild from the severe forms of pancreatitis in a ratio similar to that of adults²¹. This marker should be used on a larger scale by paediatricians in clinical practice in order to select the severe cases of acute pancreatitis.

We also found that the haematocrit value and the serum calcium and potassium concentrations were significantly different in patients with the severe form as compared to those with the mild form of acute pancreatitis. Regarding the haematocrit values, our results are in contrast with those previously reported in adults²²; we found that haematocrit values were significantly lower in children with severe acute pancreatitis than in those with mild pancreatitis. Further studies are necessary to confirm the hypothesis that these parameters may be useful in child care by allowing early identification of those with severe forms of acute pancreatitis.

Surgery was performed in 7 patients (14%) being elective in 5 of them, thus showing that the treatment of acute pancreatitis is mainly conservative in paediatric patients.

In our study, the overall mortality rate was 2%; while the mortality rate of the 9 patients with severe acute pancreatitis was 11%. In the review article by Mader and McHugh¹⁵ in which 10 studies carried out from 1956 to 1986 were considered, the mortality rate in paediatric acute pancreatitis ranged from 0 to 27% with a mean value of 14%. This may be due to various reasons; probably the early diagnosis of acute pancreatitis together with intensive medical treatment may have had some beneficial effects in lowering the mortality in the present series.

Finally, the hospital stay in patients with severe acute pancreatitis was not significantly different from that of children with the mild form of the disease; this finding is similar to that previously reported in the adult Italian population¹⁴.

Although our study revealed some clinical characteristics of acute pancreatitis in Italian children, others need to be clarified by further prospective studies in order to achieve a better characterisation of the aetiology of childhood acute pancreatitis, to establish the real prevalence of the disease and to confirm the usefulness of some biochemical parameters, such as haematocrit, serum calcium and potassium concentrations in the clinical assessment of the severity of the disease.

List of abbreviations

BUN: blood urea nitrogen; CRP: C-reactive protein; HIV: human immunodeficiency virus; URL: upper reference limit.

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