



Diagnosis and Management of Pancreatitis in Childhood: A Single-Centre Experience

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Abstract

Background: Pancreatitis can be seen at any age in childhood. Therefore, it is important for pediatricians to know the diagnosis and the management of pancreatitis.

Objectives: The aim of this study was to evaluate the etiological factors, clinical features and management of pancreatitis in children.

Methods: This study included hospitalized children who were diagnosed with pancreatitis. The clinical presentations, laboratory analyses, radiological features, etiologies and treatments were recorded.

Results: A total of 59 pancreatic attacks were recorded in 41 patients. The most common symptoms were abdominal pain and vomiting, and the most common etiological cause was idiopathic. Approximately 22% of the patients had acute recurrent episodes. Somatostatin was used to treat 61% of the attacks; however, it did not reduce the time to recovery after an attack when compared to those patients who did not use somatostatin ($P = 0.36$). The white blood cell counts and urea and calcium levels were significantly different between those patients who did and did not use somatostatin. Seventeen (28.8%) of the pancreatitis attacks were determined to be severe. Moreover, a mutation in the cystic fibrosis transmembrane conductance regulator was detected in two patients with recurrent pancreatitis.

Conclusions: Fever and irritability can be signs of pancreatitis in infants and toddlers. In our cases, the somatostatin treatment was not effective in terms of the time to recovery after an attack.

Keywords: Pancreatitis, Child, Somatostatin

1. Background

Pancreatitis is not necessarily a rare disease in children, but in severe cases it may be life threatening. Acute pancreatitis (AP) is a necroinflammatory disease of the pancreas, and the clinical approach for AP has been evolving based primarily on adult studies (1, 2). In recent years, some studies have examined the incidence and etiology of pancreatitis in children, and several have characterized the clinical presentation and management of these cases (3-5). The incidence of AP is 3.6 - 13.2 cases per 100,000 children per year, which approaches the incidence of pancreatitis in adults (3, 6, 7).

The common causes of AP in children include infections, abdominal trauma, drug induced injury, cholelithiasis, structural anomalies of the biliary/pancreatic junction and metabolic and systemic diseases, as well as idiopathic causes (8). The clinical manifestations can differ depend-

ing on the age of the child and the underlying etiology. Many diagnoses and treatment regimens are based on the consensus conferences and evidence in adults, but new articles have been published on pancreatitis in children in recent years (7, 9). However, the effects of the treatment modalities on the length of the hospital stay and treatment success should be discussed.

2. Objectives

We have reported the demographic, clinical and laboratory data, as well as the etiological factors and management of children with pancreatitis.

3. Methods

This retrospective study was performed for 41 patients (1 month to 17 years old) with 59 attacks who were diag-

nosed with pancreatitis. These children were admitted to the Tepecik training and research hospital, Izmir, Turkey, pediatric gastroenterology clinic from May 2014 to September 2016. They were hospitalized and followed up in the pediatric gastroenterology department. The patients' data were collected from the hospital records retrospectively.

The patients were categorized into AP, acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) groups according to the international study group of pediatric pancreatitis: in search for a cure (INSPPIRE) (10). The patients with AP were classified as mild (no organ failure and no local/systemic complications), moderately severe (organ failure that resolved within 48 hours and/or local or systemic complications without persistent organ failure), or severe (single or multiple persistent organ failures for > 48 hours). The patients were evaluated for severe pancreatitis according to the Ministry of Health, Labour and Welfare of Japan (JPN) scoring system (9, 11).

The patients were evaluated in terms of their gender, age, clinical findings, laboratory analysis results, imaging tests, treatments, treatment responses, etiologies and pancreatic attack features. Ethical approval was obtained from the ethics committee of the Tepecik Training and Research Hospital (03.05.2017/1).

The data were assessed using descriptive statistics, including the numbers, percentages distributions, median, means and standard deviations. The Student's t tests were used for comparing the data according to the parametric variables. The data was evaluated via SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0, released 2011; IBM Corp., Armonk, NY, USA), and a P value of less than 0.05 was considered to be significant.

4. Results

The mean age of the patients was 9.3 ± 5.3 years and 26 (63.4%) of the patients were female. The most common symptoms were abdominal pain (83%) and vomiting (63.4%), and 53.7% of the patients were admitted with both symptoms. The other patient complaints included fever (12.2%), nausea (4.9%), irritability (7.3%) and diarrhea (2.4%). The youngest patients were 1 and 3 months, 1, 1.5 and 2 years old and complained of irritability and/or fever. Thirty-two (78%) of the patients had only one AP attack. ARP was present in 9 (22%) of the patients, and two of them had CP findings. The etiological causes were idiopathic (48.8%), abdominal trauma (7.3%), viral infection (4.9%), systemic disease (shock-sepsis) (12.2%), metabolic (hypertriglyceridemia) (7.3%), choledochal cyst (2.4%), pancreatic divisum (2.4%), pancreatic divisum with cystic fibrosis (2.4%), choledochal cyst with hypertriglyceridemia (2.4%), cystic fibrosis (2.4%), choledocholithiasis (7.3%) and

drug induced injury (2.4%). All of the patients with ARP had complaints of abdominal pain during each pancreatic attack. The characteristics of the patients with ARP are shown in Table 1.

Forty-one patients experienced a total of 59 pancreatic attacks, and the median duration between the attacks was 6 months (minimum 1, maximum 58 months). Seventeen (28.8%) of the pancreatic attacks were evaluated as severe, while the others were mild to moderate. No mortalities due to pancreatitis occurred in our patients. The laboratory analyses of the patients with pancreatitis are shown in Table 2.

The amylase level was at least 3 times the normal level during 45 of the pancreatic attacks (76.3%), and the lipase level was at least 3 times the normal level during 49 of them (83.1%). The amylase and lipase values normalized within a median of 10 days (minimum 2, maximum 92 days) after an attack. The median hospital stay was 10 days (minimum 3, maximum 250 days). Somatostatin was used in 36 (61%) of the pancreatic attacks (1-3 mcg/kg/hour, maximum 3 mg, intravenous infusion), with a mean of 9.1 ± 8.7 days, and 17 of the pancreatic attacks using somatostatin were severe. The laboratory analyses used in the evaluation of severe pancreatitis scoring system and treatment durations for the patients with and without somatostatin are shown in Table 3. Overall, the somatostatin treatment did not reduce the time to recovery after an attack when compared to those patients who did not use somatostatin ($P = 0.36$). Antibiotic therapy (cefotaxime or cefuroxime or piperacillin or amikacine) was used in 37 (62.7%) of the pancreatic attacks, with a mean of 10.2 ± 5.8 days, while somatostatin and antibiotic treatments were used in all of the severe pancreatitis attacks.

Oral feeding was stopped in all of the patients during hospitalization and was restarted in a median of 4 days (minimum 2, maximum 48 days) after an attack. Total parenteral nutrition was initiated in 19 (32.2%) of the pancreatic attacks and administered for a mean of 15.1 ± 12.6 days. Oral nutrition was initiated with a low-fat diet in 42 (71.2%) of the pancreatic attacks, with enteral nutrition in 12 (20.3%), breast feeding in 1 (1.7%) and a low-fat diet and enteral nutrition together in 2 (3.4%).

All of the patients were evaluated by ultrasonography (USG). The results indicated a normal pancreatic parenchyma in 17 (41.5%) cases, but the pancreas could not be evaluated in 9 (22%) of the cases. The patients with ARP and CP and the patients with poor response to treatment were evaluated for possible malformations and complications with advanced imaging techniques. Abdominal computed tomography (CT) was used to evaluate 16 (39%) patients and revealed the formation of pseudocysts in one patient, which were not detected on the USG. In 5 (12.2%) of the

Table 1. The Characteristics of the Patients with Recurrent Pancreatitis

| Patients with Recurrent Pancreatitis | Number of Attacks | Etiology |
|--------------------------------------|-------------------|-------------------------------------|
| 1. | 2 | Idiopathic |
| 2. | 2 | Idiopathic |
| 3. | 2 | Idiopathic |
| 4. | 2 | Choledochal cyst |
| 5. | 3 | Idiopathic |
| 6. | 3 | Hypertriglyceridemia |
| 7. | 5 | Pancreas divisium |
| 8. | 6 | Pancreas divisium + cystic fibrosis |
| 9. | 2 | Cystic fibrosis |

Table 2. The Laboratory Analyses of the Patients with Pancreatitis

| | Normal Range | Mean \pm SD | Minimum - Maximum |
|--------------------|--------------|---------------------|-------------------|
| Amylase (U/L) | 28 - 100 | 1098 \pm 1289 | 102 - 8050 |
| Lipase (U/L) | 3 - 39 | 1728 \pm 1532 | 154 - 8000 |
| ALT (U/L) | 0 - 50 | 38.4 \pm 64.6 | 5 - 305 |
| AST (U/L) | 0 - 50 | 52.5 \pm 68.6 | 7 - 415 |
| GGT (IU/L) | 3 - 22 | 55.2 \pm 11.8 | 2 - 662 |
| Urea (mg/dL) | 0 - 38 | 27.4 \pm 19.6 | 3 - 123 |
| Creatinine (mg/dL) | 0.5 - 1.2 | 0.8 \pm 0.7 | 0.1 - 4.5 |
| Glucose (mg/dL) | 60 - 100 | 106.4 \pm 31.4 | 8 - 218 |
| Calcium (mg/dL) | 8.8 - 10.8 | 9.3 \pm 0.6 | 7.9 - 10.6 |
| CRP (mg/L) | 0 - 5 | 31.9 \pm 44.8 | 0.01 - 181 |
| WBC (uL) | 4.2 - 10.6 | 11712 \pm 5117 | 5000 - 24900 |
| Hematocrite (%) | 43.3 - 53.7 | 36.3 \pm 6.2 | 19 - 52 |
| Platelet (uL) | 140 - 400 | 280864 \pm 102430 | 26000 - 554000 |
| MCV (fL) | 80 - 97 | 79.3 \pm 6.1 | 62 - 98 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; MCV, mean corpuscular volume; SD, standard deviation; WBC, white blood cells.

patients, the pancreatitis findings were detected by CT but not by USG. A magnetic resonance cholangiopancreatography was performed in 28 (68.3%) of the patients. A pancreatic divisium was detected in two patients, a choledochal cyst in two and dilatation of the pancreatic duct in four.

A genetics analysis of the patients with recurrent pancreatitis revealed no mutations in the cationic trypsinogen (PRSS1) or serine protease inhibitor, Kazal type 1 (SPINK1), but homozygous mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) were detected in two patients.

5. Discussion

Pancreatitis exhibits a wide clinical spectrum in children and may present as AP, ARP or CP (8). AP is the most common pathological entity affecting the pancreas in children, and the diagnosis of AP is based on a combination of clinical findings, biochemical tests and imaging studies (10, 12) The two classical symptoms of AP are abdominal pain and nausea/vomiting. The most common clinical presentations of the patients in our study were abdominal pain and vomiting, too. Infants and toddlers tend to present with irritability and less often with abdominal pain and vomiting. In our study, five infants and toddlers

Table 3. The Laboratory Analyses Used in the Evaluation of Severe Pancreatitis Scoring System and Treatment Durations for the Patients with and Without Somatostatin

| | Using Somatostatin | | P |
|---|--------------------|--------------|-------|
| | Yes | No | |
| Time to recovery of amylase and lipase (days) | 15.1 ± 14.2 | 10.9 ± 19.7 | 0.36 |
| Amylase (U/L) | 899 ± 792 | 1169 ± 1696 | 0.08 |
| Lipase (U/L) | 1810 ± 1338 | 1574 ± 1875 | 0.42 |
| WBC (uL) | 12250 ± 5896 | 10870 ± 3538 | 0.023 |
| Urea (mg/dL) | 24 ± 10.5 | 32.3 ± 28 | 0.011 |
| Creatinine (mg/dL) | 0.78 ± 0.6 | 0.9 ± 0.83 | 0.32 |
| Calcium (mg/dL) | 9.4 ± 0.45 | 9.2 ± 0.8 | 0.007 |
| CRP (mg/L) | 37.5 ± 49.5 | 22.4 ± 34.6 | 0.14 |

Abbreviations: CRP, C-reactive protein; WBC, white blood cells.

had irritability and/or fever; therefore, it is important to consider pancreatitis in infants who present with these clinical findings.

Children with AP may present with ARP, which can eventually progress to CP. ARP occurs in 15% - 36% of the children with AP (8). In our study, ARP was observed in 22% of the patients, and two had CP findings. A biliary pathology, drug induced injury and idiopathic, genetic and structural pancreatic disorders, as well as metabolic and systemic diseases can all be causes of ARP. It is well documented that mutations in the PRSS1, CFTR and SPINK1 genes can cause hereditary pancreatitis. However, there is no clear distinction between those diseases that cause recurrent attacks of AP and those causing CP (8). An evaluation of PRSS1, SPINK1 and CFTR mutations may be beneficial in children with a family history of ARP or CP. For example, Wejnarska et al reported that 260 children with CP were screened for PRSS1, SPINK1 and CFTR, and the mutation most frequently found was in the SPINK1 gene (13). In one study involving 301 children, 155 had ARP and 146 had CP, and those patients with PRSS1 or SPINK1 mutations were more likely to present with CP when compared with ARP (14). The highest number of attacks among our patients with ARP occurred in the patient with a CFTR mutation and pancreatic divisum. The etiologies in the other patients with ARP included pancreatic divisum, choledochal cyst, hypertriglyceridemia and cystic fibrosis.

A transabdominal USG is a useful tool and can be used as a first-line imaging study to confirm pancreatitis in children with clinically and laboratory-suspected pancreatitis (15). In addition, the USG findings are often normal in children with AP, particularly in early or mild cases (12). The pancreatic parenchyma was normal on the USG in 41.5% of the patients. Therefore, CT is more sensitive than USG for

detecting AP and grading its severity (12). In 5 (12.2%) of our patients, the pancreatitis findings were detected by CT but not by USG.

The initial treatment for AP is to withhold oral food or fluid intake in order to allow the pancreas to rest (12). However, parenteral fluid and electrolyte supplementation and treatment to relieve pain and prevent infection are provided during this time (11, 12). In addition, AP often produces intense and persistent pain, so pain control is required (16, 17). One recent retrospective study suggested that feeding can be started orally, upon admission, without increasing the pain severity and length of the hospital stay (18). Those researchers also suggested that the fat content in the food did not seem to be associated with increased pain levels or the length of the hospital stay (18). Oral feeding in all of the patients was stopped initially, and oral nutrition was initiated as a low-fat diet in 71.2% in our cases. In our retrospective study, the effects of nutrition on the pain and length of the stay were not assessed because there were no patients initially followed by oral feeding and separated by fat content. So, there is a need for prospective studies regarding nutrition in the treatment of childhood pancreatitis.

Somatostatin analogues are powerful inhibitors of exocrine pancreatic secretions and cholecystokinin production (19). Several studies have evaluated the effects of octreotide on the incidence of clinical pancreatitis after endoscopic retrograde cholangiopancreatography and the postoperative complications, such as a pancreatic duct fistula following a pancreaticoduodenectomy or a pancreatic transplantation (20, 21). However, the effectiveness of octreotide in reducing AP complications has not been demonstrated (22). In addition, there is no role for somatostatin or its analogues in the treatment of AP. In our study,

no effect on the recovery time after an attack was observed in the patients who were given somatostatin. Moreover, enzyme replacement therapy is not routinely prescribed to resolve the AP phase, except in select situations. Pancreatic enzyme replacement therapy was only used in two patients with CFTR mutations in our cases.

A rapid and accurate assessment of the severity of pancreatitis is useful for selecting the appropriate initial treatment and predicting a prognosis. According to the JPN scoring system, the presence of three or more of the nine criteria indicates severe pancreatitis, with a 96% specificity and 80% sensitivity in children (9, 11). When we compared the laboratory analyses of the patients who did and did not use somatostatin, it was found that the white blood cell, urea and calcium values in the JPN scoring system were significantly different. One limitation of our study was its retrospective design, also some of the data required for the JPN scoring system assessment were not available for every patient.

The incidence of infectious complications and the mortality rate are low in mild cases of AP, and prophylactic antibiotics are not usually necessary. However, antibiotics should be considered in mild cases if the severity increases or complications such as cholangitis develop. Antibiotics can reduce infectious pancreatitis complications and improve the prognosis in severe cases (23). In our study, antibiotics were used in all of the cases of severe pancreatitis, and were also used in some of the moderate pancreatitis attacks. Complications, such as abscesses and cholangitis, were not observed in any of the cases using antibiotics. When the complications related to pancreatitis were evaluated, a pseudocyst was observed in only the case of post-traumatic pancreatitis, in which the patient was given somatostatin and did not require surgical intervention.

Pancreatitis is a common problem in children and should be considered in the differential diagnosis of abdominal pain. However, it should be kept in mind that infants and young children may present with very different clinical findings from those of adults. In this study, it was seen that the somatostatin therapy did not have a significant effect on the recovery time of the pancreatic attacks. Those patients with recurrent AP attacks should be thoroughly assessed for the etiology and appropriately treated to prevent complications and CP. However, there are controversial issues in the management of pancreatitis in childhood, so there is a need for more prospective studies of children with pancreatitis regarding their treatment and management.

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