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ORIGINAL PAPER

Aetiology and clinical characteristics of first episode of acute pancreatitis in children

Martyna N. Sokół[1], Joanna E. Radulska[1], Aleksandra Żaczek[1], Paulina Krawiec[2], Elżbieta Pac-Kożuchowska[2]

[1]Students' Scientific Group at the Department of Paediatrics and Gastroenterology, Medical University of Lublin, Poland
[2]Department of Paediatrics and Gastroenterology, Medical University of Lublin, Poland

ABSTRACT

Aim of the study: Although the recognition of acute pancreatitis in children has been increasing over the last decades, knowledge this condition is limited. Thus, we aimed to evaluate the aetiology and clinical course of the first episode of acute pancreatitis in children.

Material and methods: We retrospectively analysed medical records of patients hospitalized due to the first episode of acute pancreatitis in the Department of Paediatrics and Gastroenterology, Medical University of Lublin, from January 2011 to December 2019. The analysis took into account the age and sex of patients, clinical symptoms, abnormalities in physical examination, past and family history data, and results of laboratory and imaging tests. The review of consecutive hospitalizations of patients from the study group was carried out to assess the number of recurrences of pancreatitis in the analysed period.

Results: The study group consisted of 72 patients, including 37 boys and 35 girls. The age of patients ranged from 2 to 18 years, with a median of 12 years. The vast majority (62%) of acute pancreatitis cases were diagnosed in the latter 4 years of the study period. In 43% of patients, acute pancreatitis was of idiopathic origin, followed by infectious (22%), toxic (18%), and biliary (8%) aetiology. The most common initial symptoms included abdominal pain (93%), vomiting (66%), and nausea (28%). In the study period recurrence of acute pancreatitis occurred in one-third of the children.

Conclusions: Paediatric acute pancreatitis is an increasing health care issue with various aetiologies. Acute pancreatitis should be considered in every child with acute abdominal pain, vomiting, or nausea. Further studies are needed to determine the risk factors of recurrent acute pancreatitis.

KEY WORDS:

abdominal pain, pancreatitis, cholelithiasis, child, adolescent.

INTRODUCTION

Acute pancreatitis (AP) is a rarely diagnosed disease in the paediatric population. However, in the last 20-25 years there has been a significant increase in the number of cases of acute pancreatitis among children and adolescents [1-6].

Regardless of the aetiological factor, the process of inflammation in the course of acute pancreatitis follows a common pathomechanism, the essence of which is the early pathological activation of intra-pancreatic proenzymes (mainly trypsinogen). Triggering of the enzymatic cascade results in self-destruction of the organ cells and the induction of pro-inflammatory cytokines synthesis, which may lead to tissue damage outside the pancreatic parenchyma and a generalized inflammatory reaction. In most cases, the inflammatory process is confined to the

ADDRESS FOR CORRESPONDENCE:

Paulina Krawiec, Department of Paediatrics and Gastroenterology, Medical University of Lublin, Al. Racławickie 1, 20-059 Lublin, Poland, e-mail: paulinakrawiec@umlub.pl

pancreas (acute oedematous pancreatitis). More rarely necrosis in the pancreas and surrounding tissues occurs (necrotizing pancreatitis) [7].

The aetiological factors of AP in children appear to be much more diverse than in adults. While in adults the most common causes of AP are diseases of the gallbladder and biliary tract, and alcohol [8], in children a clear order of aetiological factors is difficult to establish because their frequency differs in various studies. The most common causes of acute pancreatitis in children are idiopathic, drugs, gallstones, infections, and injuries [1, 2, 7, 9, 10]. Less frequent are metabolic causes, anatomical anomalies of the pancreatic duct, and genetic factors, including mutations in the *PRSS1*, *SPINK1*, *CFTR*, and *AA* genes [11].

The clinical symptoms of acute pancreatitis range from mild abdominal pain to multi-organ failure. The most common clinical manifestation in the paediatric population (80-95% of cases) is acute abdominal pain, most often located in the epigastrium [3, 11-14]. Pain radiation to the lumbar region, often described in the literature, is rarely seen in children [14]. Nausea and vomiting are slightly less common in children in the course of AP [15, 16]. Other symptoms include fever and abdominal distension, which are more common in younger children [17].

The first classification of acute pancreatitis was established in 1992 in Atlanta [18]. The Atlanta Classification, modified in 2012, is currently in force, according to which AP is recognized when at least 2 of the following criteria are met:

- acute abdominal pain in the epigastrium, often radiating to the back,
- serum lipase or serum amylase activity > 3-times above the upper limit of normal value,
- pathological changes in imaging studies characteristic of AP [18].

Modified in 2012, the Atlanta classification [18] is also used to diagnose AP in children, despite significant differences in the aetiology, clinical picture, and course of acute pancreatitis in the paediatric population compared to adults.

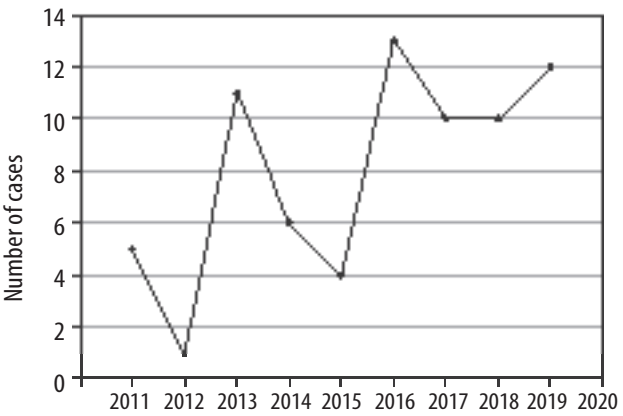

FIGURE 1. Number of patients hospitalized due to the first episode of acute pancreatitis at the Department of Paediatrics and Gastroenterology, Medical University of Lublin in 2011-2019

Despite the distinctness of the symptoms described in children and adults in the course of AP, no classification has been developed so far for the diagnosis of AP in the paediatric population. Existing hypotheses about the cause of the increase in AP incidence in children do not explain this phenomenon. The aim of the study was to analyse the aetiological factors and clinical course of the first episode of AP in children.

MATERIAL AND METHODS

We performed a retrospective analysis of medical files of patients hospitalized due to the first episode of acute pancreatitis at the Department of Paediatrics and Gastroenterology, Medical University of Lublin from 01/01/2011 to 31/12/2019. From the hospital database of patients, people were selected with the underlying or comorbid diagnosis of K85 according to the International Statistical Classification of Diseases and Health Problems ICD-10.

The analysis took into account the age and sex of patients, clinical symptoms, abnormalities in physical examination, past and family history data, and results of laboratory and imaging tests. Moreover, a review of consecutive hospitalizations of patients from the study group was carried out to assess the number of recurrences of pancreatitis in the analysed period. Recurrent AP was defined as the occurrence of ≥ 2 episodes of pancreatitis.

Statistical analysis was carried out with the use of Statistica StatSoft v.13. The values of the analysed parameters due to the nominal measurement scale were characterized by the number and percentage, while due to the quotient measurement scale they were characterized by the arithmetic mean and standard deviation as well as the median and the range of variation. The Mann-Whitney *U* test was used to compare 2 independent groups. To assess the existence of differences between the compared groups or the existence of a relationship between the analysed non-measurable parameters, the homogeneity or independence test for qualitative features was used. The level of significance was $p < 0.05$.

The study was approved by the Bioethics Committee at the Medical University of Lublin (No. KE-0254-116-2020).

RESULTS

In the study period, from 01/01/2011 to 31/12/2019, 72 patients were hospitalized in the Department of Paediatrics and Gastroenterology due to the first episode of acute pancreatitis. Figure 1 shows the number of hospitalizations due to the first episode of AP in individual years. In the analysed period, most of the hospitalizations (n = 45; 62%) took place within the last 4 years of the analysed period.

There were 37 (51%) boys and 35 (49%) girls in the study group. The mean age of the patients was 11.25 ±4.8

years. The youngest patient was 2 years old, and the oldest patient was 18 (median 12 years). The mean age of boys was 11.1 ±4.5 years (median 12.25 years), and girls 11.4 ±5.1 years (median 11.5 years). There was no statistical difference between the age of boys and girls in the study group ($Z = -0.15$; $p = 0.6$). The majority of children had normal nutritional status (46; 63.9%). Undernutrition was recognised in 8 (11.1%), overweight in 10 (13.9%), and obesity in 8 (11.1%) children.

Majority of the children did not have any comorbid chronic diseases ($n = 56$; 78%). The most common reported comorbidities were epilepsy ($n = 6$) and ulcerative colitis ($n = 6$). Individual patients had other diseases, including Crohn's disease ($n = 1$), short bowel syndrome ($n = 1$), VACTERL association ($n = 1$), and Smith-Lemli-Opitz syndrome ($n = 1$).

In 31 (43%) patients AP was of idiopathic origin. In 16 (22%) cases, AP was immediately preceded or associated with the infection. In most patients, mild upper airway infection was recognized before pancreatitis onset. In our department influenza was confirmed in one child, pneumonia due to *Mycoplasma pneumoniae* infection in one child, and *Herpes simplex* virus infection in one child.

In 13 (18%) patients, AP was toxic: in 10 (14%) cases AP was associated with taking drugs, most often valproic acid ($n = 5$) and azathioprine ($n = 2$). In the latter 3 (4%) cases toxic AP was preceded by alcohol consumption. In 6 cases (8%) AP had obstructive aetiology due to gallstone disease confirmed by imaging tests. In 4 cases (5%), the acute pancreatic episode was preceded by an abundant, in 2 cases (3%) by abdominal surgery, and in 1 (1%) by an abdominal injury. Dyslipidaemia or calcium-phosphate metabolism disorders were not recognized in any of the children. In 2 (3%) patients chronic pancreatitis was confirmed in a first-degree relative.

Figure 2 shows the symptoms reported by patients on admission to hospital. Figure 3 shows the abnormalities in the physical examination of patients on the day of admission to hospital.

On admission, lipase activity in the blood serum exceeding 3 times the upper limit of normal value was found in 71 (98.5) patients, and > 3-fold increase in the level of serum amylase activity was observed in 45 (62.5%) patients.

The majority of the patients had elevated parameters of inflammation: WBC > 10,000/µl ($n = 44$; 61%) and/or CRP > 10 mg/l ($n = 46$; 64%). Elevated liver function tests were found in about 1/3 of patients: including elevated ALT in 21 patients (29%), GGTP in 20 patients (28%), and elevated bilirubin in 17 patients (24%).

All children underwent ultrasound examination of the abdominal cavity. Abnormalities were found in 73.6% of cases ($n = 53$). The most frequently observed changes were pancreatic enlargement ($n = 28$; 38.9%), changes in pancreatic echogenicity ($n = 24$; 33.3%), presence of peripancreatic fluid ($n = 12$; 16.7%), and pancreatic oedema ($n = 11$; 15.3%).

The changes in the bile ducts recorded on ultrasound included biliary dilatation ($n = 12$; 16.6%), ductal stones ($n = 4$; 5%), gallbladder stones ($n = 6$; 8%), and the presence of gallbladder sludge ($n = 4$; 5%). Four patients with choledocholithiasis required endoscopic retrograde cholangiopancreatography.

In 10 cases (14%) the diagnostics was extended to computed tomography (CT), but only in 2 cases necrotic changes in the pancreas were found.

Chest radiography (X-ray) was performed in 15 patients (21%). In 8 patients, the presence of fluid in the pleural cavity was found, and in 4 patients – interstitial changes in the lungs. In the remaining 3 patients there were no abnormalities in the chest X-ray.

Most of the acute pancreatitis cases were mild to moderate. Only in one case did the patient's condition require

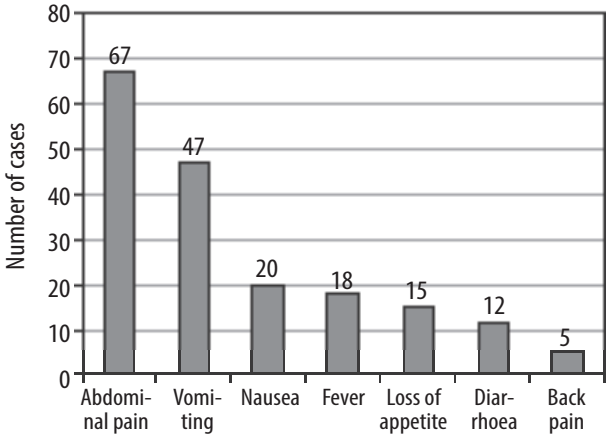

FIGURE 2. Clinical symptoms in patients hospitalized due to the first episode of AP at the Department of Paediatrics and Gastroenterology, Medical University of Lublin (one patient can complain of more than one symptom)

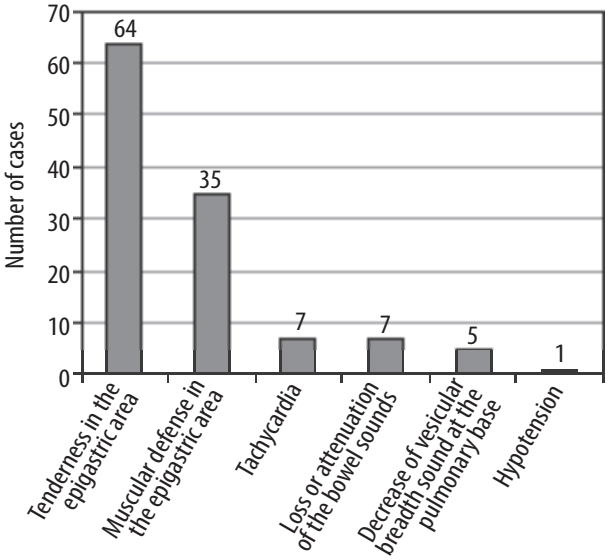

FIGURE 3. Signs in the physical examination of patients hospitalized for the first episode of AP at the Department of Paediatrics and Gastroenterology, Medical University of Lublin (one patient can present with more than one sign)

treatment in an intensive care unit due to acute respiratory distress syndrome. The shortest hospitalization was 1 day and the longest was 33 days. The mean length of hospitalization was 11.3 ±6.8 days (median 11 days).

A second or subsequent episode of acute pancreatitis was experienced by 22 patients (30.6%). Among children with recurrent pancreatitis, there were 8 (36%) boys and 14 (64%) girls. However, in the group of patients with episodic AP, there were 29 (58%) boys and 21 (42%) girls. This difference was not statistically significant ($\chi^2 = 2.86$; $p = 0.09$). The mean age of patients with recurrent pancreatitis was 10 ±4.5 years (median: 9 years), and patients with episodic acute pancreatitis had an average age of 12 ±5 years (median: 13.5 years). Although the patients with recurrent AP were younger than those with episodic AP, this difference was not statistically significant ($Z = 1.82$; $p = 0.07$). We found that 7 children had genetic predisposition to recurrent pancreatitis, including 3 (13.6%) children with mutation in the *SPINK1* gene, 2 (9%) children in both *SPINK1* and *CTRC* genes, 1 (4.5%) child in the *CFTR* gene, and 1 (4.5%) child in the *CTRC* gene. Moreover, among children with recurrent pancreatitis, one had annular pancreas and one had cholelithiasis. Within the study period, in 13 (59.1%) children recurrent pancreatitis remained idiopathic.

DISCUSSION

In this 9-year retrospective study, we observed that the majority (62%) of the first episodes of AP occurred within the last 4 years of the analysed period. The actual incidence of AP in the paediatric population is unknown. However, it seems that it may be underestimated due to non-specific symptoms of the disease [14]. Despite this, recently in many studies an increase in the incidence of acute pancreatitis in the paediatric population has been observed [1, 6-9]. This phenomenon was first described in American studies by Lopez in 2002 (an increase in the number of patients with acute pancreatitis from 5 to 113 per year in the years 1993-1998) [4]. An upward trend in the incidence of AP in the population of American children was also observed by Werlin *et al.* [3]. An increase in the number of AP cases among children was also noted in studies from other countries [2, 5, 6, 19]. Sanchez-Ramirez *et al.* reported a 16-fold increase in the incidence of AP in children in Mexico in 1990-2005 [2]. Morinville *et al.* showed an increase in the incidence of AP in children from 28 to 141 cases per year in 1993-2004 [5]. This tendency was also confirmed in the study by Nydegger *et al.* (increase from 2.5 to 3.5/100,000/year in 1993-2002) [6] and Cheng *et al.* (increase from 2.33 to 3.07/100,000/year in the years 2000-2013) [19]. However, Grzybowska-Chlebowczyk *et al.* did not show a clear rising trend in their study. In the years 2004-2013, the number of hospitalizations due to acute pancreatitis ranged from 3 to 14. It can be noted, however, that the frequency of hospitalizations showed an upward trend in the years 2006-2011, and in the next 2 years of the analysed period it decreased significantly [20].

The reason for the increase in the diagnosis of AP, observed in many studies, is unknown. The greater number of identified cases may reflect the true increase in the frequency of AP in the paediatric population or result from the greater awareness of physicians about AP in children, thus including this disease in the differential diagnosis of abdominal pain, vomiting, and nausea in children [3]. In addition, the availability of laboratory and imaging tests has significantly improved in the past few years. However, Lopez suggested that the increase in blood lipase and amylase measurements is not associated with an increase in the diagnosis of acute pancreatitis [4]. In his study, it was shown that despite the reduction in the number of pancreatic enzyme activity tests in the emergency department, the number of patients with AP increased [4]. This fact may indicate a real increase in pancreatitis morbidity in children.

In our study, the mean age of the patients (11.25 years) was slightly lower than in the literature (11.6-13.6 years) [3, 19-21]. In the study group, boys and girls were of comparable age. However, Cheng *et al.* showed that boys were statistically significantly ($p = 0.003$) older (mean age = 12.25 years) than girls (mean age = 11.55 years) [19].

In the study group, the incidence of AP was comparable among girls and boys. Similar observations were found in other studies, inter alia, by Cheng *et al.* [19], Kandula and Lowe [16], and Alabdulkareem *et al.* [21]. On the other hand, Nydegger *et al.* noted a greater dominance of the male sex (58.4%) [6]. In the study by Grzybowska-Chlebowczyk *et al.* [20], a slight dominance of girls (53%) was found among children with pancreatitis.

The aetiological factors of acute pancreatitis in children are varied and, in many cases, difficult or impossible to determine (idiopathic pancreatitis) [1, 2, 7, 9, 10]. In our study, the aetiology of AP was mostly similar to that described in the literature. In most cases ($n = 31$; 43%) the cause of the first episode of acute pancreatitis could not be determined. A similar percentage of idiopathic AP in the Polish population was recorded by Grzybowska-Chlebowczyk (43.1%) [20]. The number of patients with an unidentified cause of an AP episode in the literature is 8-43% [1-3, 13-16, 19-28].

The second most common aetiological factor in the study population was the relationship of AP with infection. Almost a quarter of children with the first episode of AP developed an infection in the period immediately preceding or during the onset of AP. In the literature, the proportion of AP cases related to infection varies between 8% (3) and 29% [16]. Not all authors consider the infectious factor as a potential cause of AP in their analyses [20, 21, 28]. Establishing a clear cause-and-effect relationship between infection and acute pancreatitis is difficult. In some cases, drugs used in the infection may also be a causative agent of AP.

Toxic acute pancreatitis affected patients who used drugs on a permanent basis and those who consumed alcohol, and it was the third most common cause of acute pancreatitis in our study group. The incidence of acute pancreatitis caused by treatment of other diseases is reported in the literature at the level of 4.0-25.6% [1, 2, 19-21, 25-27], and in our population it concerned 14% of patients. Drugs that can trigger an episode of acute pancreatitis include valproic acid, steroids, some antibiotics, mesalamine, and azathioprine [1, 8]. Interpreting the causal relationship between drugs used and AP is difficult and should be approached with caution. It should be emphasized that some systemic diseases themselves may also predispose to pancreatitis [9, 28].

In the literature, the incidence of biliary aetiology is 9-30% [2, 3, 15, 19-21, 25-27]. In our study, an episode of acute pancreatitis was less frequently associated with diseases of the biliary tract (8%).

In our study, only in one patient (2%), AP was preceded by an abdominal injury, while in the literature the incidence of post-traumatic pancreatitis ranges from 8% in infants and young children [16] to as much as 46% [25]. This difference may be due to the fact that our study included only patients from the Department of Paediatrics and Gastroenterology. Patients after injuries may be hospitalized in surgical wards or intensive care units.

The most frequently reported symptom in the course of AP in children is abdominal pain. The percentage of patients reporting this symptom in the literature is 68-95% [2, 6, 10, 13, 14, 16, 20-25, 27]. Pain radiating to the back, characteristic of AP in the adult population, is a symptom rarely reported by children [14]. In our study, 93% of patients on admission reported pain in the abdominal cavity, and only 7% complained of pain radiating to the back. Vomiting, described in the literature as the second most common symptom of AP [2, 3, 10, 13, 14, 16, 20-27], was reported by 66% of children. Nausea was less frequent than vomiting. The clinical picture of AP in older children is different than in younger children. Younger children are less likely to report abdominal pain (43-46% vs. 68-93%) [15, 16] and nausea and vomiting (28% vs. 70%) [16]. Infants and toddlers show fewer clinical symptoms than older children, and therefore the diagnosis of pancreatitis may be difficult in this age group. It should be remembered that crying, irritability, or anxiety may be indirect symptoms of abdominal pain in the youngest group of patients.

Elevated serum lipase levels are more sensitive and specific in the diagnosis of acute pancreatitis than amylase, the elevated levels of which may be due to several other causes unrelated to pancreatic disease [3, 27]. In our study, as in the literature [1-3, 13, 21, 25], the most frequent elevated marker in children with AP was pancreatic lipase (98.5%).

According to the modified Atlanta criteria, abdominal CT with intravenous contrast is the gold standard for imaging examinations. The AP classification (interstitial oedematous pancreatitis and necrotizing pancreatitis) is also based on the result of this study [18]. However, in most cases, transabdominal ultrasound in the hands of an experienced radiologist is a sufficient screening imaging test for the diagnosis of acute pancreatitis in children. Changes in the ultrasound examination suggesting AP include oedema, changes in the echogenicity of the pancreatic parenchyma, and the presence of fluid collections [9]. However, it should be emphasized that the correct image of the pancreas on ultrasound does not exclude AP. Due to the high availability, lack of potential side effects, and relatively low cost of performance, ultrasound can also be used to monitor the course of the disease, especially in uncomplicated cases [29, 30]. Moreover, ultrasound has an advantage over computed tomography in the diagnosis of gallstone disease, which is one of the causes of AP [9, 31]. In the study group, all children underwent abdominal ultrasound. Abnormalities in the image of the pancreas were noted more often (73.6%) than in other studies (25-67%) [1-3, 20, 23].

Computed tomography of the abdominal cavity should be performed in the case of uncertain diagnosis and severe course, especially when pancreatic necrosis is suspected, preferably between 72 and 96 hours after the onset of clinical symptoms [29, 30, 32]. Computed tomography was performed on patients with a more severe course of AP. In our study, the oedematous form of AP was present in most children. Similar results were observed by Sanchez-Ramirez *et al.* [2].

Contrary to the adult population, in whom several scales for estimating the severity of the course of AP are available (Ranson's, Glasgow, and Apache II scale), reliable prognostic systems for children are lacking [30].

Most often, acute pancreatitis is mild (without organ failure) or moderate (temporary organ failure up to 48 hours), but the course of the disease is unpredictable. There is rarely a severe course, with chronic organ failure requiring intensive therapy [1, 3, 13, 16, 20]. In our patient population, there was no death resulting from AP and its complications or any other causes. Only one patient with the first episode of AP required hospitalization in the intensive care unit.

Recurrent pancreatitis is characterized by the occurrence of 2 or more episodes of acute pancreatitis during the lifetime of the patient with no evidence of chronic pancreatitis. The incidence of recurrent acute pancreatitis in children concerns 12-35% of patients [1-3, 20, 21, 26, 28-31]. In the studied group, in the analysed period, relapses occurred in 30.6% of cases. In our study, boys were slightly more likely to have more than one episode of acute pancreatitis (58%), while in the study by Randall *et al.*, recurrent pancreatitis was more common in girls (57%) [31]. In this population, younger children were slightly more prone to recurrent pancreatitis. In patients with recurrent pancreatitis, the causes should be looked for, including the presence of congenital pancreatic and biliary tract defects, the

autoimmune process, and genetic predisposition (mutations in the *CFTR*, *PRSS1*, *SPINK* 1, *CTRC*, *CPA1* genes) [33].

It should be emphasized that our work may have some limitations due to its retrospective nature. Moreover, some limitations of inference may result from the fact that the study analysed patients hospitalized only in the gastroenterological ward of a paediatric hospital.

CONCLUSIONS

To conclude, paediatric AP is an increasing health care issue, and it should be considered in the differential diagnosis of acute abdominal pain. Although in many cases the aetiology of AP remains unknown, important causes of AP are infections, medications, and cholelithiasis. Ultrasound examination of the abdomen may be used as a screening imaging study in AP suspicion. In the study group, recurrence of AP affected one-third of children, particularly the youngest ones. Further studies are needed to determine risk factors of recurrent AP and to identify prognostic factors of AP in childhood.

DISCLOSURE

The authors declare no conflicts of interest.

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