Original article

Etiology and clinical characteristics of pediatric acute pancreatitis in Saudi Arabia: a 20-year experience from a single tertiary center

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ABSTRACT

Background: Cases of acute pancreatitis (AP) have increased among pediatric populations worldwide; however, the natural course of this condition in Saudi Arabia was unknown.

Aim: To report the characteristics as well as outcomes of pediatric AP.

Patients and methods: A retrospective chart review study was conducted to include acute pancreatitis in patients < 19 years. The period was from 1994 until 2015. Demographic, clinical, laboratory, imaging and outcome data were collected and analyzed.

Results: 50 patients (n = 26; 52% males vs. n = 24; 48% females) were included. The mean age at diagnosis was 11.6 years. The mean length of hospital stay was 10.5 days. 9 (18%) patients had a recurrence of AP and 4 (8%) had complications. Idiopathic AP was the most frequent etiology (n = 21; 42%). Followed by cholelithiasis (n = 11; 22%). 2 patients (4%) had drug-induced AP, where one was taking isoniazid and the other had taken a large amount of erythromycin, amoxicillin and ibuprofen. 2 choledochal cysts complicated by AP (4%). Pancreaticobiliary diseases, as a complete entity, accounted for 34% (n = 17). Clinically, abdominal pain (n = 47; 94%) and vomiting (n = 38; 76%) were most commonly encountered. KUB was non-diagnostic in all patients. No patient died during their admission.

Conclusion: Although still relatively uncommon in Saudi Arabia, there are on average 2–3 cases of pediatric AP diagnosed annually in our institution. Isoniazid and choledochal cysts are rare causes of AP and were reported in the study.

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1. Introduction

Inflammation of the pancreas (pancreatitis) occurs as a result of the spillage and autodigestion of the pancreatic parenchyma by the digestive enzymes. Acute pancreatitis (AP) is characterized by the presence of inflammatory cells and results in reversible structural and functional changes over a short duration. In contrast, chronic pancreatitis causes irreversible changes that ultimately result in fibrosis and loss of exocrine and/or endocrine function [1].

According to the International Study Group of Pediatric Pancreatitis: in Search for a Cure (INSPPIRE), two of three criteria must be fulfilled to diagnose AP in the pediatric population; namely, abdominal pain, serum amylase or lipase levels that are three times the upper normal limit and radiological findings diagnostic of AP [2,3].

AP is a rare disorder among individuals aged younger than 20 years, the number of pediatric AP cases recorded worldwide has increased dramatically over the past few years [4]. A 10-year American study estimated that the incidence of primary AP among children had increased from 6350 cases to 9561 cases between 2000 and 2009, representing a 51% increase [5]. A retrospective chart review conducted in the United States of America

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(USA) found that the incidence of first pediatric AP admission increased from 2.3 per 100,000 children in 1993 to 13.2 per 100,000 children in 2004 [6]. The authors concluded that the observed rise might reflect increased testing for AP among the pediatric population.

To date, no national or regional studies have been conducted in Saudi Arabia to assess pediatric AP. Therefore, the aim of the current study was to describe the etiology, clinical characteristics of this disease among Saudi children and increase clinical awareness of pediatric AP.

2. Methods

A 20-year retrospective chart review study was conducted at King Abdullah Specialized Children Hospital and King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia. Institutional Review Board (IRB) was obtained from the King Abdullah International Medical Research Center (KAIMRC), National Guard Health Affairs, Riyadh, Saudi Arabia, with a reference number of RC16/110/R.

Medical records were reviewed to identify all pediatric patients (age <15 years) who were diagnosed with primary AP between 1994 and 2015. Patients with missing data were excluded from the analysis. We defined age groups as the following: pre-schooler (0–5 years), schooler (6–11 years) and adolescent (12–19 years).

Demographic, clinical and outcome data were evaluated to establish shared features among patients with primary AP in our population. Imaging techniques, including kidney–ureter–bladder (KUB) plain film, ultrasonography (US) and computed tomography (CT), were also evaluated.

3. Statistical analysis

Statistical analysis was performed using JMP version 12 (SAS Institute, Cary, NC, USA). Continuous and categorical variables are given as the mean ± standard deviation (SD) and as the number and percentage, respectively. The Student’s t-test was used to assess the differences in means. Differences in categorical variables were analyzed with the chi-squared test. Analysis of variance (ANOVA) was used to assess continuous variables. A test with P value of less than .05 was statistically significant.

4. Results

A total of 50 patients (n = 26; 52% males vs. n = 24; 48% females) were included. The mean age at diagnosis was 11.6 years. Patients were diagnosed with primary AP during the present study at a rate of two to three cases per year. (Baseline demographics are presented in Table 1).

Idiopathic AP was the most frequent etiology (n = 21; 42%), followed by gallstones (n = 11; 22%) (Summary of etiologies is shown in Table 2). 2 (4%) had drug-induced AP, where one was taking isoniazid while the other had ingested a large amount of isoniazid. 6 patients (12) had endoscopic retrograde cholangiopancreatography (ERCP). One patient (16%) underwent ERCP for removal of common bile duct (CBD) stone, while another was diagnosed with choledochal cyst involving the CBD. (See Radiographic Findings of Pediatric Acute Pancreatitis in Table 3).

The mean length of stay (LOS) was 10.5 days (2–62), median 6. The pre-schooler group had a mean LOS of 12 days, whereas the schooler and adolescent groups had a mean LOS of 15 and 12 days, respectively. Patients who were admitted to the pediatric Intensive Care Unit (PICU) had a mean LOS in the unit of 2.7 (1–7), median 2. The pre-schooler group had a mean LOS of 5.5 days, and the schooler and adolescent groups had a mean LOS of 2.75 and 2 days, respectively. Patients who presented with abdominal pain and fever had significantly longer PICU stay (P = .0007, P = .0211, respectively).

18% (n = 9) experienced recurrence of AP. 8% (n = 4) had complications; 2 (33.3%) acute respiratory distress syndrome, 1 (16.6%) septic shock, 1 (16.6%) hypocalcemia, 1 (16.6%) pseudocyst and 1 (16.6%) pancreatic necrosis. No patients died due to AP.

5. Discussion

The present study aimed to define a baseline for pediatric AP in Riyadh, Saudi Arabia, by describing the etiological factors, clinical presentation, relevant laboratory tests and imaging findings among all cases of primary disease identified at our institute. Pediatric AP was diagnosed at a rate of approximately two to three cases per year in the present study.

The etiology of AP among children is variable. A US-based study published in 1999 found that 25% of pediatric AP cases are of unknown etiology, with 13%–33% of cases attributed to blunt trauma, making it the most common cause of pancreatitis among both adults and children [7]. However, a study published in 2013 claimed that pediatric AP due to trauma is less common than previously
of gallstones. Unlike western in our present study were either idiopathic or had occurred because was the most frequent cause of pediatric AP among Japanese, recognizable effects on the course and etiology of pediatric AP [9].

In terms of racial differences, Majbar et al. reported that United pancreaticobiliary disorders accounted for 42% and 34%, respectively. Though idiopathic causes were more common, pancreaticobiliary diseases contributed to a huge bulk of the AP cases. However, our analysis showed that idiopathic AP and one cause in our analysis, gallstones were associated with 22% of pediatric AP. Suzuki et al. stated that biliary diseases, including gallstones, was much more common in eastern Asian Population [10]. Even though it is not the number one cause in our analysis, gallstones were associated with 22% of pediatric AP. However, our analysis showed that idiopathic AP and pancreaticobiliary disorders accounted for 42% and 34%, respectively. Though idiopathic causes were more common, pancreaticobiliary diseases contributed to a huge bulk of the AP cases. In terms of racial differences, Majbar et al. reported that United Kingdom children of Pakistani origin have a seven-fold increased risk of developing AP compared to white children [11]. This could have not been assessed by us, as all patients were Arabs/Saudis.

The diagnosis of idiopathic AP is not quite reassuring, as some genetic and/or congenital anomalies could be the reason. Physicians should reasonably exhaust resources to exclude all possible causes of AP before labelling it as idiopathic. Our review does not show any genetic causes, despite the fact some patients had multiple recurrences. Childhood AP trend is increasing. This should alert healthcare providers, i.e pediatricians, to fully work-up patients before making such diagnosis. However, Ballinger et al. stated that 1 in 31 patients with first attack of idiopathic AP suffers from another one in median of 36 moths [12]. This suggests that looking for other underlying cause of AP after only the 1st attack is not cost-effective, as most of them will not have another. This is quite similar to our study where 9 out 50 had subsequent attacks. In conclusion, there is no clear guidelines to when to work up a patient for other underlying causes and when not. This study demonstrated this lack of clear pathway to assist in patients' diagnosis.

Furthermore, we believe that it is highly unlikely that some of the common causes mentioned in the literature were missed. i.e. trauma, due to the fact that the study was conducted in a tertiary trauma center, where AP post motor vehicle accident or handle-bar injury was unlikely to be missed. In addition, some other form of trauma, such as child abuse, is hard to diagnose especially in our culture.

On the other hand, one 5.5-year-old male presented with AP as result isoniazid (INH) ingestion. INH is relatively safe tuberculosis chemoprophylaxis and INH-induced AP is uncommon, however, there have been case reports of INH-induced AP around the world in both children and adults [13–15]. INH-induced hepatitis (21/100,000) is well recognized since the early 1970s, however, INH-induced AP is less common and not well described in the literature [15]. Badalov and colleagues had built a classification drug-induced AP [16]. Their system had 4 classes, in which isoniazid had been classified into Class I. They defined Class I as “include medications in which at least 1 case report described a recurrence of acute pancreatitis with a rechallenge with the drug”. To our knowledge, this is the first time INH-induced AP has been reported in Saudi Arabia.

Another case of drug-induced acute pancreatitis (DIAP) was shown in our analysis. A 17-year-old female who had ingested multiple medication, including erythromycin, amoxicillin and ibuprofen. These medications have been reported in the global literature as an etiology of AP [17–19]. There is an obvious shortage in the local literature of DIAP, where clinicians and researchers of our nation should aid in filling this gap.

The association between choledochal cysts and acute pancreatitis is well-established [20,21]. Acute pancreatitis tends to reoccur in the presence of any type of choledochal cysts. Saluja and

### Table 2
Summary of etiologies.

| Etiology, n (%) | Male | Female | 0-5 yr | 6-12 yr | 12-19 yr | Total |
|----------------|------|--------|-------|--------|---------|-------|
| Idiopathic     | 10 (47.6) | 11 (52.3) | 2 (9.5) | 6 (28.5) | 13 (61.9) | 21 (42) |
| Gallstone      | 6 (54.5) | 5 (45.5) | 0      | 2 (18.1) | 9 (81.9) | 11 (22) |
| Pancreatic Divum | 1 (33.3) | 2 (66.6) | 1 (33.3) | 0      | 2 (66.6) | 3 (6) |
| DKA*           | 1 (50)  | 1 (50)  | 0      | 1 (50)  | 1 (50)  | 2 (4)  |
| Drug-Induced   | 1 (50)  | 1 (50)  | 0      | 1 (50)  | 1 (50)  | 2 (4)  |
| Familial Hyperlipidaemia | 1 (50) | 1 (50) | 1 (50) | 1 (50) | 0      | 2 (4)  |
| Post ERCPb     | 2 (100) | 0      | 0      | 2 (100) | 2 (4)  | 4 (8)  |
| Choledochal Cyst | 1 (50) | 1 (50) | 1 (50) | 1 (50) | 0      | 2 (4)  |
| Familial Hypertriglyceridemia | 1 (100) | 0     | 0      | 1 (100) | 0      | 1 (2)  |
| Herbs          | 0      | 1 (100) | 0      | 0      | 1 (100) | 1 (2)  |
| CBD* sludge    | 0      | 1 (100) | 0      | 0      | 1 (100) | 1 (2)  |
| Trauma         | 1 (100) | 0      | 1 (100) | 0      | 0      | 1 (2)  |
| Viral Infection | 1 (100) | 0      | 0      | 0      | 1 (100) | 1 (2)  |

* DKA: Diabetic Ketoacidosis.
* ERCP: Endoscopic Retrograde Cholangiopancreatography.
* CBD: Common Bile Duct.

### Table 3
Main radiographic findings of pediatric acute pancreatitis.

| Radiological findings, n (%) | US (n (%) | CT (n (%)) |
|-----------------------------|-----------|-----------|
| Normal                      | 14 (22.5) | 3 (8.1)   |
| Enlarged, bulky pancreas    | 11 (17.7) | 8 (21.6)  |
| Acute peripancreatic fluid collections | 1 (1.6) | 9 (24.3)  |
| Gallstone                   | 9 (14.5)  |           |
| Peritoneal fluid            | 6 (9.6)   | 3 (8.1)   |
| Dilated CBD                 | 4 (6.4)   |           |
| Dilated intrahepatic duct   | 3 (4.8)   |           |
| Dilated gallbladder         | 3 (4.8)   |           |
| Necrotic pancreatitis       |           | 2 (5.4)   |
| pseudocyst                  | 1 (1.6)   | 2 (5.4)   |
| Dilated pancreatic duct     |           | 2 (5.4)   |
| Choledochal cyst            |           | 1 (2.7)   |
| Budd-Chiari Syndrome        | 1 (1.6)   |           |
| Choledocholithiasis         | 1 (1.6)   |           |

* a 2 patients had ERCP and 1 patient had MRCP.
* b US; Ultrasound.
* c CT; Computed Topography.
* d CBD: Common Bile Duct.
colleagues had reported 6 cases of chronic pancreatitis in the presence of choledochal cysts. Interestingly, pancreatitis occurrence, weather acute or chronic, with choledochal cysts are less likely to be reported in the Middle East, North Africa, North America and/or Europe. Most of the reports of this phenome has been described in eastern and central Asia, such as China, Japan and India [20–23]. In Saudi Arabia, Crankson et al. reported a case of choledochal cyst in 10-month-old boy, however, the patient was surgically managed without developing pancreatitis [24]. Another case report form Saudi Arabia has been described by Al Saleem et al., however, pancreatitis occurrence was not described [25]. To our knowledge, this is the first time where choledochal cysts and acute pancreatitis have reported in Saudi Arabia.

Most patients included in the current analysis complained of abdominal pain at presentation, with or without vomiting/nausea. One of the INSPIRE criteria for AP diagnosis was almost always fulfilled by our patients, where abdominal pain was, by far, the most common symptom (n = 47; 96%). Pediatric AP has a better prognosis than AP diagnosed among adults [26]. Compared to pediatric patients without AP, US children with AP have longer LOS (median 4 days vs. 2 days), higher financial costs ($22,663 vs. $11,364) and a higher mortality rate (7.6 per 100,000 individuals vs. 2.7 per 100,000 individuals) [5]. Pediatric AP has decreased LOS, increased costs and decreased mortality rates. Our study shows AP LOS had a mean of 10.5 days and median of 6 days.

A US-based study found that both AP patients with pseudocysts and those who were malnourished had longer LOS than other patients [27]. Furthermore, African American children had a greater need for pediatric intensive care unit (PICU) admission than white children (18% vs. 7%, respectively white) [27]. In the current series, there were statistically significant differences in patients who presented with abdominal pain and fever and length of PICU admission (P = .0007, P = .0211, respectively).

No clear guideline or protocol is currently available for working-up a patient with suspicion of pediatric AP, nor when to admit. Ultrasonography detected abnormal findings in approximately 50% of the patients included in the present study, with an enlarged pancreas the most frequent finding. US findings were confirmed using CT. KUB was of no use in diagnosing children with AP. Summary of pediatric AP characteristics from different studies is shown in Table 4.

The limitation is that it is a retrospective study in a one center, hence the small number of cases. We recommend multicenter study to fully assess the characteristics of AP in children. Another limitation is the lack of proper documentation in patients’ charts, especially the older ones. This is most apparent in this study where viral cause of AP was not documented in the file. The main strength of the present study was it is the first report from our nation to shed the light on pediatric AP. Also, our paper report one of the rarest causes of AP, i.e., INH-induced AP and choledochal cysts, both locally and globally.

6. Conclusion

Although still relatively uncommon in Saudi Arabia, approximately 2–3 cases of pediatric AP were diagnosed annually at our institution. Idiopathic AP and pancreaticobiliary disorders accounted for 42% and 34%, respectively. Isoniazid-induced AP and choledochal cysts are rare causes, even though, they were reported in the study.

Conflicts of interest

None.

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