Etiology of Acute Recurrent Pancreatitis in Vietnamese Children: an Initial Report

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ABSTRACT

Objectives: The aim of this study was to describe the epidemiological characteristics of acute recurrent pancreatitis (ARP) among children who were admitted at Children’s Hospital 2, Ho Chi Minh City, Vietnam, from May 2014 to May 2019.

Methods: Authors presented Case series study.

Results: A total of 33 cases met the criteria for study inclusion. The mean age of first onset 7.3 ± 4.4 years (range, 1.4–15 years), the male to female ratio was 18:15 (1.2:1). The median number of ARP admissions per patient was 3 (range, 2–14), and the median time between ARP-related hospitalization was 168 days (range, 82–240 days). The chief complaint upon hospitalization was abdominal pain, accounting for 96.9% of cases, vomiting in 87.9% of cases, and severe ARP was observed in 24% of cases. All patients underwent magnetic resonance cholangiopancreatography (MRCP), and abdominal computed tomography (CT) scans. Genetic testing was performed in 14 of 33 cases, and 5 cases had at least 1 mutation, whereas 9 were negative. The most common etiology of ARP was biliary tract disease, in 17 cases (51.5%; 11 choledochal cysts, 6 gallstones), abnormalities of the pancreas were observed in 18.2% (abnormalities of pancreatic structures in 3 cases), hypertriglyceridemia and metabolic disease were observed in 6.1% of cases, and genetic mutations were identified in 15.2% of cases. Conclusion: ARP is not a rare disease, and ARP patients may be admitted to the hospital many times. The chief complaints resulting in hospitalization were abdominal pain and vomiting. The most common causes were biliary tract diseases (bile duct cysts in 33.3% and gallstones in 18.2% of cases), with abnormalities of the pancreatic structure identified in 9.1% of cases, and genetic mutations detected in 15.2% of patients.

Keywords: Acute recurrent pancreatitis, etiology, choledochal cyst, genes mutation, structural abnormalities of the pancreas.

1. INTRODUCTION

Acute recurrent pancreatitis (ARP) is an acute and repetitive inflammatory process of the pancreas. The term “acute recurrent pancreatitis” was first described by Doubilet et al. in 1948 (1). According to previous reports, approximately 30% of AP patients will experience recurrence (2, 3). Among children, according to Park et al, the percentage of patients with ARP having acute pancreatitis (AP) was about 15.3% (4). And the results of two studies by Benifla et al and Pezzilli et al reported that this rate was 10% - 20% (5, 6).

Several different criteria exist for ARP diagnosis; however, most members of the Pediatric Gastroenterology Association agree with the following definition and criteria. ARP is defined as 2 episodes of AP associated with the resolution of pain (≥ 1 month between episodes) or the normalization of pancreatic enzymes and the resolution of pain between episodes, irrespective of time interval (7).

Identifying the underlying causes of ARP can be quite difficult. According to Lucidi et al, the rate of pediatric idiopathic ARP was approximately 26.9% (8). To diagnose the underlying causes, many factors, including clinical symptoms and some modern diagnostic methods, such as ultrasound (US), endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP), must be examined. The performance of tests and procedures, such as ERCP and MRCP, are considered to be important contributors to the diagnoses of the underlying causes and treatment of ARP in many cases (9). In recent studies, ERCP was determined to be a significant factor in the identification and treatment of the underlying causes of ARP (10, 11).
Currently, at Pediatric hospitals in Vietnam, diagnosing the underlying causes of ARP has been challenging. No reports have examined the distribution of contributing factors that result in ARP development in Vietnam. Many pediatric patients are hospitalized several times without receiving a diagnosis for the underlying cause of ARP. The treatments provided during each hospital stay primarily treat the symptoms, with few solutions for the thorough treatment of the underlying cause, which can adversely affect the patients’ quality of life.

2. AIM
To contribute to the initial survey and assessment of the underlying causes of ARP among Vietnamese children, our aim with this study was to describe the epidemiological characteristics associated with ARP in Vietnamese children.

3. METHODS
Research method: Case series study.

Ethical statement: This study was performed as a retrospective study, extracted from health records, without affecting patients’ health. This study was approved by the Medical Ethics Committee of the Children's Hospital 2.

Study subjects: All patients with ARP treated at Children's Hospital 2 from May 2014 to May 2019.

Sampling criteria: All children young than 16 years old who met the criteria for ARP diagnosis.

According to the Atlanta criteria and INSPIRE Consortium (International Study Group of Pediatric Pancreatitis: In search for a cure) definitions, a diagnosis of AP requires 2 of the following 3 elements: clinical symptoms, including abdominal pain, nausea, vomiting, or back pain; serum levels of pancreatic amylase or lipase 3 times the normal upper limit; and radiographic evidence of AP, including pancreatic edema on US or computed tomography (CT) (7, 12, 13).

ARP was defined as 2 episodes of AP, accompanied by the resolution of pain (≥ 1 month between episodes) or the normalization of pancreatic enzymes and the resolution of pain in between episodes, irrespective of time interval (7, 8, 12).

Exclusion criteria: Pediatric patients who lacked adequate medical records (epidemiological, clinical, laboratory tests, treatment) were excluded.

Data processing and analysis
To perform statistical analysis, the continuous variables were expressed as the mean ± standard deviation or the median with interquartile range (IQR), according to the normality of distribution meanwhile the nominal variables were introduced as frequency and percentage (%). All data were analyzed by SPSS software for Windows, version 20.0 (SPSS Inc, Chicago, Ill).

4. RESULTS
A total of 33 pediatric patients with cause-identified ARP were included in this study, who were hospitalized a total of 132 times. Table 1 shows the epidemiology, clinical manifestations, and laboratory parameters.

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4. RESULTS
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| Characteristics | Results, n = 33 |
|-----------------|----------------|
| Age at first hospitalization (years) | 7.3 ± 4.4 |
| Male/female | 1.2/1 |
| Average number of hospitalizations (time) | 3 (2–14) |
| Number of hospitalizations (n, %) | 2 times 8 (24.2) >2–10 times 23 (69.8) >10 times 2 (6) |
| Median interval between admissions (days) | 168 (82–240) |
| Reasons for hospitalization (n, %): | |
| Abdominal pain | 32 (96.9) |
| Vomiting | 29 (87.9) |
| Others | 1 (3) |
| BMI (n, %): | |
| Normal | 18 (54.5) |
| <2 SD by age | 9 (27.3) |
| >2 SD by age | 6 (18.2) |
| Severity | |
| Mild, Moderate | 25 (75.7) |
| Severe | 8 (24.3) |
| Imaging studies performed (n, %): | |
| Abdominal Ultrasound | 33 (100) |
| Abdominal CT scan | 33 (100) |
| MRCP | 33 (100) |
| ERCP | 1 (3) |
| Abdominal X-ray | 4 (12.1) |
| Chest X-ray | 4 (12.1) |
| EUS | 0 |
| Serum amylase (U/L) | 1021 ± 173 |
| Serum lipase (U/L) | 983 ± 183 |
| Genetic | 14 (42.4) |
| SPKIN1 | 3 (9) |
| PRSS1 | 2 (6) |
| CFTR | 0 |
| CTRC | 0 |
| Average length of hospitalization (days) | 9.5 (6.5–12) |
| (range: 4–50) | |

Table 1. Epidemiology, clinical manifestations, and laboratory parameters

The study results showed that the average age of the first hospitalization was 7.3 ± 4.4 years. The youngest age was 17 months, whereas the oldest age was 15 years. Males accounted for 18 patients (54.5%), whereas females accounted for 15 patients (45.5%). The male/female ratio was 1.2/1. The median number of hospitalizations was 3 (range: 2–14), with the majority of cases hospitalized between 2 and 10 times (69.8%), and 2 cases experienced hospitalized more than 10 times. The mean time between hospitalizations was 168 days (range: 82–240 days), with the shortest and longest intervals being 31 days and 24 months plus ten days, respectively. The most common reason for hospitalization was abdominal pain, in 32 cases (96.9%), followed by vomiting (87.9%), with 3% hospitalized for other reasons. A total of 24% of patients experienced severe episodes of pancreatitis while hospitalized. All patients in the study were tested for serum amylase and serum lipase, with recorded levels greater than three times the normal upper limit in all patients. The mean lipase concentration was 983 ± 183 U/L, and the mean amylase concentration was 1,021 ± 173 U/L. All pediatric patients included in this
Table 2. The causes of ARP (n=33)

| Causes                              | Frequency (Percentage %) |
|-------------------------------------|--------------------------|
| Biliary tract:                      |                          |
| Bile duct cysts                     | 11 (33.3)                |
| Gallstones, gallbladder             | 6 (18.2)                 |
| Pancreatic:                         |                          |
| Pancreatic stones                   | 3 (9.1)                  |
| Pancreas divisum                    | 1 (3)                    |
| Pancreatic duct stenosis            | 1 (3)                    |
| Disease of the isthmus of the pancreas | 1 (3)                |
| Hypertriglyceridemia, metabolic disease | 2 (6.1)                 |
| Post-intervention, surgery in the biliary tract | 3 (9.1)                |
| Genetic mutation                    | 5 (15.2)                 |

5. DISCUSSION

Our study results showed that the average age of hospitalized pediatric ARP patients was 7.3 ± 4.4 years, with the youngest age recorded at 17 months and the oldest at 15 years. These results differed from those reported by Pant et al, who reported a median age of 11 years (IQR 7–14 years) (14). Our study included 18 males (54.5%) and 15 females (45.5%), with a male/female ratio of 1.2/1. The median number of hospitalizations was 3 (range: 2–14), which was the same as the study by Poddar et al, who reported an average number of hospitalizations of 3 (IQR, 2–4) times (15). We observed a mean duration between hospitalizations of 168 days (82–240), compared with Pant et al, who reported a mean duration of 86 days (37–218) (14). These differences are likely due to differences in the conditions of care and treatment between Vietnam and developed countries. It may also reflect differences in the sample size among distinct studies. The primary cause for hospitalization was recorded as abdominal pain, in 32 cases (96.9%), followed by vomiting (87.9%), with 3% hospitalized for other reasons, which was similar to the results by Sánchez-Ramírez et al (16). During hospitalization, 24% of patients experienced severe episodes of pancreatitis, which was higher than the study by Sweeney et al, who reported only 11% of patients with severe episodes (17).

All pediatric patients in our study underwent ultrasound, abdominal CT, and MRCP scans after each hospital admission. According to Kumar et al, MRCP was the most commonly used imaging modality (18). Among the 14/33 pediatric patients who were tested for genetic mutations, 5/14 cases were found to harbor genetic mutations (3/14 SPINK1 and 2/14 PRSS1). The major types of mutations were segment mutations, point mutations, and changes in amino acids. None of the children in our study were found to harbor mutations in CTRC or CFTR. These figures are lower than the results reported by Saito et al, who indicated that 39.1% of Japanese children with ARP and chronic pancreatitis harbored at least one genetic mutation (19). Another study, by Xia et al, on genetic mutations in Chinese children with ARP and chronic pancreatitis reported that 65.2% of patients had at least one gene mutation (20). The difference between our study and the studies by Saito et al (19) and Xia et al (20) may be due to differences in the sampling method and the small number of gene mutations examined in our patients (we only examined four genes, whereas Xiao et al examined ten genes) (19, 20).

The most commonly identified underlying causes were pancreatic and gallbladder diseases, with biliary duct cysts identified in 11 cases, gallstones in 6 cases, pancreatic stones in 3 cases and pancreatic structural abnormalities, such as pancreas divisum (1 case), pancreatic duct stenosis (1 case), and disease of the pancreatic isthmus (1 case), which each accounted for 3% of cases. Genetic mutations were identified in 5 of 33 patients (15.2%), including mutations in CTRC or cystic fibrosis transmembrane conductance regulator (CFTR). These figures are lower than the results reported by Sweeney et al, who indicated that 39.1% of Japanese children with ARP and chronic pancreatitis harbored at least one genetic mutation (19). Another study, by Xia et al, on genetic mutations in Chinese children with ARP and chronic pancreatitis reported that 65.2% of patients had at least one gene mutation (20). The difference between our study and the studies by Saito et al (19) and Xia et al (20) may be due to differences in the sampling method and the small number of gene mutations examined in our patients (we only examined four genes, whereas Xiao et al examined ten genes) (19, 20).

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The most commonly identified underlying causes were pancreatic and gallbladder diseases, with biliary duct cysts identified in 11 cases, gallstones in 6 cases, pancreatic stones in 3 cases, and pancreatic structural abnormalities, such as pancreas divisum, pancreatic duct stenosis, disease of the pancreatic isthmus. The study by Lucidi et al indicated that ARP in Italian children was associated with structural abnormalities in 19.2% of children (8). The results of a recent study reported by Kumar et al revealed that the most common risk for the development of ARP or chronic pancreatitis was pancreatic structure abnormalities (18). Other rare external causes of ARP, such as hypertriglyceridemia and metabolic diseases, were reported at similar rates in our and other studies. Genetic mutations were previously considered to be ARP risk factors, and some researchers have suggested that genetic mutation may represent an underlying cause of this disease. Two mutant genes that are often detected in studies of ARP are SPINK1 and PRSS1, which account for 15.2% of the underlying causes of the disease. According to a report by Xia et al, who studied a group of patients with ARP and chronic pancreatitis, among the ten mutant genes they detected, SPINK1 and PRSS1 accounted for a high proportion of the identified mutations. According to the above evidence, testing for genetic mutations in children with ARP may be necessary to identify the underlying risk factors and causes.
According to Lee et al, the frequencies of SPINK1 or PRSS1 gene mutations are relatively high among Korean children with ARP and chronic pancreatitis (21). The most common causes of ARP in adults are alcohol and tobacco use, whereas among children, as mentioned in this present study, the prominent causes include structural abnormalities and gallstones or pancreatic stones. In addition, genetic mutations have continued to receive increasing attention (22). In the future, additional studies examining the underlying genetic causes among Vietnamese children with ARP will hopefully provide a more detailed perspective.

6. DISCUSSION

ARP is not a rare disease and may require hospitalization several times due to abdominal pain and vomiting. The most common causes of ARP among Vietnamese children are gall stones and pancreatic stones and abnormalities in the structure of the gallbladder and pancreas, such as bile duct cysts, pancreas divisum, pancreatic duct stenosis, or pathology of the pancreatic isthmus. Other rare causes include metabolic disease and hypertriglyceridemia. The expansion of ERCP indications for ARP remains necessary, and in the near future, EUS should be deployed to screen for ARP causes. In addition, testing for genetic mutations will also be helpful for identifying the causes of ARP, particularly for SPINK1 and PRSS1, which are two common genetic mutations associated with ARP.

Abbreviations; AP Acute pancreatitis; ARP Acute recurrent pancreatitis; CFTR Cystic fibrosis transmembrane conductance regulator; CT computed tomography; CTRC Chymotrypsin C; ERCP endoscopic retrograde cholangiopancreatography; EUS endoscopic ultrasound; INSPIRE INternational Study Group of Pediatric Pancreatitis: In Search for a Cure; IQR interquartile range; MRCP magnetic resonance cholangiopancreatography; PRSSI Cationic trypsinogen; SPINK1 Serine protease inhibitor Kazal-type 1.

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Ethical approval and Declaration of patient consent: Medical Ethics Committee of the Children's Hospital 2 approved this retrospective study.

Author's contribution: NMD and HVT contributed equally to this article as co-first authors. HQT and HQP gave a substantial contribution in acquisition, analysis, and data interpretation. HQP and NMD had a prepared, drafted, and revised article critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. Doubilet H, Mulholland JH. Recurrent Acute Pancreatitis: Observations on Etiology and Surgical Treatment. Ann Surg. 1948; 128(4): 609-636.
2. Venu RP, Geenen JE, Hogan W, Stone J, Johnson GK, Soergel K. Idiopathic recurrent pancreatitis. An approach to diagnosis and treatment. Dig Dis Sci. 1989 Jan; 34(1): 56-60.
3. Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done? World J Gastroenterol. 2008; 14(7): 1007-1010.
4. Park A, Latif SU, Shah AU, Tian J, Werlin S, Hsiao A, Pashankar D, Bhandari V, Nagar A, Husain SZ. Changing referral trends of acute pancreatitis in children: A 12-year single-center analysis. J Pediatr Gastroenterol Nutr. 2009 Sep; 49(3): 316-322.
5. Benifla M, Weizman Z. Acute pancreatitis in childhood: analysis of literature data. J Clin Gastroenterol. 2003; 37(2): 169-172.
6. Pezzilli R, Morselli-Labate AM, Castellano E, et al. Acute pancreatitis in children. An Italian multicentre study. Dig Liver Dis. 2002; 34(5): 343-348.
7. Morinville WD, Husain SZ, Bai H, Barth B, Alhoush B, Durie PR, Freedman SD, Himes R, Lowe ME, Pohl J, Werlin S, Wilschanski M, Ur A; INSPIRE Group. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr. 2012; 55(3): 261-265.
8. Lucidi V, Alghisi F, Dall’Oglio L, et al. The etiology of acute recurrent pancreatitis in children: a challenge for pediatricians. Pancreas. 2011; 40(4): 517-521.
9. Sajith KG, Chacko A, Dutta AK. Recurrent acute pancreatitis: clinical profile and an approach to diagnosis. Dig Dis Sci. 2010; 55(12): 3610-3616.
10. Agarwal J, Nageshwar Reddy D, et al. ERCP in the management of pancreatic diseases in children. Gastrointest Endosc. 2014; 79(2): 271-278.
11. Fugazza A, Bizzarri B, Gaiani F, et al. The role of endoscopic ultrasound in children with PancreatoBilliary and gastrointestinal disorders: a single center series and review of the literature. BMC Pediatr. 2017; 17(1): 203.
12. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62(1): 102-111.
13. Abu-El-Haija M, Kumar S, Szabo F, et al. Classification of Acute Pancreatitis in the Pediatric Population: Clinical Report From the NASPGHAN Pancreas Committee. J Pediatr Gastroenterol Nutr. 2017; 64(6): 984-990.
14. Pant C, Sferra TJ, Lee BR, Cojcin JT, Olyaei M. Acute Recurrent Pancreatitis in Children: A Study From the Pediatric Health Information System. J Pediatr Gastroenterol Nutr. 2016; 62(3): 450-452.
15. Poddar U, Yachha SK, Borkar V, Srivastava A. Is acute recurrent pancreatitis in children a precursor of chronic pancreatitis? A long-term follow-up study of 93 cases. Dig Liver Dis. 2017; 49(7): 796-801.
16. Sánchez-Ramírez CA, Larrosa-Haro A, Flores-Martínez S, Sánchez-Corona J, Villa-Gómez A, Macías-Rosales R. Acute and recurrent pancreatitis in children: etiological factors. Acta Paediatr. 2007 Apr; 96(4): 534-537.
17. SweeneyKF, Lin TK, Nathan JD, et al. Rapid Progression of Acute Pancreatitis to Acute Recurrent Pancreatitis in Children. J Pediatr Gastroenterol Nutr. 2019; 68(1): 104-109.
18. Kumar S, Ooi CY, Werlin S, et al. Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis: Lessons From INSPIRE. JAMA Pediatr. 2016; 170(5): 562-569.
19. Saito N, Suzuki M, Sakurai Y, et al. Genetic Analysis of Japanese Children With Acute Recurrent and Chronic Pancreatitis. J Pediatr Gastroenterol Nutr. 2016; 63(4): 431-436.
20. Xiao Y, Yuan W, Yu B, et al. Targeted Gene Next-Generation Sequencing in Chinese Children with Chronic Pancreatitis and Acute Recurrent Pancreatitis. J Pediatr. 2017; 191: 158-163.
21. Lee YJ, Kim KM, Choi JH, Lee BH, Kim GH, Yoo HW. High incidence of PRSS1 and SPINK1 mutations in Korean children with acute recurrent and chronic pancreatitis. J Pediatr Gastroenterol Nutr. 2011; 52(4): 478-481.
22. Somogyi L, Martin SP, Venkatesan T, Ulrich CD 2nd. Recurrent acute pancreatitis: an algorithmic approach to identification and elimination of inciting factors. Gastroenterology. 2001; 120(3): 708-717.