COAGULATION DISORDERS IN CHILDREN WITH ACUTE PANCREATITIS AT THE VIETNAM NATIONAL CHILDREN'S HOSPITAL

Nguyen Hoai Thuong[1], Ninh Quoc Dat[1] and Nguyen Thi Viet Ha[1,2,✉]

[1]Hanoi Medical University

[2]Vietnam National Children's Hospital

Various hematological abnormalities including coagulation factor abnormalities, leukocytosis, acute hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulopathy have been reported in acute pancreatitis patients. The purpose of this descriptive cross - sectional study was to describe characteristics of coagulation disorders in 96 children with acute pancreatitis at the Vietnam National Children's Hospital. rom January 2022 to March 2023. Results showed that the mean age of children was 6.2 ± 3.2 years old, and the boy to girl ratio was 1.2 to 1, 69.8% of children had coagulation disorders. Of the 67 children who had abnormal coagulation tests, 64.2% had hypercoagulability, 35.8% had mixed hypercoagulability, 28.4% had fibrinolysis and 25.4% had disseminated intravascular coagulation. Most coagulation disorders cases showed no clinical manifestations and only 3.1% had thrombosis and hemorrhage. The factors associated with coagulopathy were hyperlipidemia and pancreatic necrosis. In conclusion, although coagulation disorders showed up in a high percentage of children with acute pancreatitis, they are difficult to be recognized based on clinical manifestations. This highlights the importance of early identification based on hemostasis testing, as it can lead to better overall management and treatment.

Keywords: Acute pancreatitis, coagulopathy, coagulation disorders, acute pancreatitic, DIC, children.

I. INTRODUCTION

Acute pancreatitis (AP) is characterized by sudden inflammatory of the pancreatic parenchyma as a result of abnormal activation of pancreatic enzymes. The severity of this disease can range from self-limiting pancreatic inflammation to presence of systemic organ dysfunctions and/or necrotizing pancreatitis with life-threatening sequelae.[1] During acute pancreatitis, inflammatory mediators (such as interleukin, tumor necrosis factor, and platelet-activating factors) are released into the systemic circulation, triggering the systemic inflammatory response syndrome and blood coagulation.[2] Various hematological abnormalities have been reported to occur in patients with acute pancreatitis. Coagulopathy symptoms in acute pancreatitis can include drops in values of hemoglobin or hematocrit, low platelet count (thrombocytopenia) and various coagulation disorders ranging from disseminated intravascular coagulopathy (DIC) to thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. These conditions can lead to the formation of the disseminated thrombus in the cardiovascular capillaries, resulting in multi-organ failure and increased risk of death.[2] Early detection of coagulopathy to determine a reasonable treatment method plays an essential role in clinical practice to reduce the spread of thrombosis, prevent multi-organ failure, and hemorrhage complications resulting in the improvement of disease prognosis. At the Vietnam National Children's Hospital, the number of children with acute pancreatitis having abnormalities on coagulation tests has been

Corresponding author: Nguyen Thi Viet Ha
Hanoi Medical University
Email: vietha@hmu.edu.vn
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increasing recently. However, there is very limited knowledge regarding coagulation abnormalities in children with pancreatic conditions. The aim of this study is to describe characteristics of coagulation disorders in children with acute pancreatitis at the Vietnam National Children's Hospital.

II. MATERIALS AND METHODS

1. Study populations

The study was conducted at the Vietnam National Children's Hospital in Hanoi, from January 2022 to March 2023. The inclusion and exclusion criteria were as follows:

Inclusion criteria: Children aged 1-16 years diagnosed with acute pancreatitis based on the 2012 revised Atlanta classification, which required two or more of the following: elevation of serum lipase or amylase levels greater than three times the upper limit of normal, imaging evidence of pancreatitis, and typical exam finding of epigastric pain and tenderness.[1] These children were closely followed and treated at the Vietnam National Children's Hospital. Coagulation tests including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer must be done for routine diagnosis and during management and monitoring period. Children and parents consent to participate in the study.

Exclusion criteria: Acute pancreatitis occurs in children diagnosed with chronic pancreatitis or recurrent pancreatitis. Children with a history of coagulopathy due to chronic liver or kidney diseases, hematology-cancer diseases, and systemic diseases or insufficient information of medical records.

2. Methods

Study design: This was a descriptive cross-sectional study of 96 children recruited through convenient sampling.

Table 1. Basic Coagulation Index Reference Range[3]

Variable	Unit	Age				
		15 days to 4 weeks	1 to 5 months	6 to 11 months	1 to 5 years	6 to 10 years	11 to 18 years
Platelet count	G/l	140-440					
PT	Seconds	9.5-12.6	9.7-12.8	9.8-13.0	9.9-13.4	10.0-14.6	10.0-14.1
APTT	Seconds	27.6-45.6	24.8-40.7	25.1-40.7	24.0-39.2	26.9-38.7	24.6-38.4
Fibrinogen	g/l	1.43-4.02	1.50-3.76	1.57-3.60	1.88-4.13	1.89-4.75	1.77-4.20
D-Dimer	ng/ ml	< 500					

PT (prothrombin time), APTT (activated partial thromboplastin time)

Table 2. States of coagulation disorders

Blood clotting disorder		Definition
Blood clotting state[4]	Normal	Values within the limits of the reference range
	Hypercoagulability	Satisfy all the criteria: increased platelet count, fibrinogen and D-Dimer
	Hypocoagulability	Satisfy all the criteria: thrombocytopenia, decrease fibrinogen, increased PT and APTT
	Mixed hypercoagulability	Both hypercoagulability and hypocoagulability
Blood fibrinolysis[4]		Satisfy all the criteria: increase D-dimer, decrease fibrinogen
DIC		DIC scale according to the International Society on Thrombosis and Haemostasis 2009[5]

Criteria for diagnosing organ dysfunction in acute pancreatitis as defined by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition 2018: respiratory failure, circulatory failure, central nervous system failure, liver failure, renal failure, multi-organ failure with more than two organ failure.[6]

Statistical analysis: The information obtained from the study was processed according to the biomedical statistical algorithm on SPSS 20.0 software. The difference was statistically significant when the p-value was < 0.05.

3. Research ethics

The study protocol was submitted to and approved by the scientific council of Hanoi Medical University and the ethics committee of the Vietnam National Children's Hospital (No. 292/BVNTW-HDDD dated February 17th, 2023).

III. RESULTS

During the study period from January 1, 2022, to March 31, 2023, we collected data from 96 children (16 months to 12 years old) diagnosed and treated with acute pancreatitis who were eligible for inclusion in the study. The research results are presented below.

Table 1. General characteristics of of children with acute pancreatitis

Characteristics		Coagulation disorders		No coagulation disorders		p
		n	%	n	%	
Mean age (years)		6.1 ± 3.2		6.6 ± 3.0		> 0.05
Gender	Boy	37	55.2	16	55.2	> 0.05
	Girl	30	44.8	13	44.8	
Average duration of treatment (days)		12.3 ± 8.1		7.2 ± 3.9		**< 0.001**

Characteristics		Coagulation disorders		No coagulation disorders		p
		n	%	n	%	
Treatment results	Recurrence	6	9.0	2	6.9	> 0.05
	Completely cure	61	91.0	27	93.1	
Total		67	69.8	29	30.2	

The rate of coagulation disorders in the study group was 69.8%. The mean age at diagnosis in the acute pancreatitis group with coagulopathy was 6.1 ± 3.2 yearsold. The ratio of boys to girls in both groups was 1.2 to 1. The mean duration of treatment in the group of acute pancreatitis with coagulopathy was longer than that of the group without coagulopathy, p < 0.001. There was no difference in treatment outcomes (death, recurrence, and complete cure) between the two groups.

Table 2. Clinical characteristics of children with acute pancreatitis according to coagulation status

Clinical characteristics	Coagulation disorders		No coagulation disorders		p
	n	%	n	%	
Intra-gastrointestinal symptoms					
Abdominal pain	62	92.5	26	89.7	> 0.05
Nausea	35	52.2	8	27.6	**0.028**
Vomiting	53	79.1	18	62.1	> 0.05
Anorexia	4	6.0	1	3.4	> 0.05
Diarrhea	12	17.9	6	20.7	> 0.05
Constipation	9	13.4	4	13.8	> 0.05
Abdominal distension	41	61.2	10	34.5	**0.025**
Ascites	1	1.5	0	0	
Abdominal wall syndrome	4	6.0	0	0	
Intra-peritoneal induction	1	1.5	0	0	
Extra-gastrointestinal symptoms					
Fever	23	34.3	10	34.5	> 0.05
Hemorrhage	1	1.5	0	0	
Thrombosis	1	1.5	0	0	
Respiratory failure	3	4.5	0	0	
Circulatory failure	1	1.5	0	0	
Multi-organ failure	1	1.5	0	0	

Clinical symptoms at the onset of the study group were very diverse, and abdominal pain was the most common symptom in both groups. Nausea and abdominal distension were more common in patients with acute pancreatitis and coagulopathy, with a p-value of 0.028 and 0.025, respectively. Most coagulation disorders cases have no clinical manifestation; only 1 case of thrombosis and 1 case of hemorrhage were recorded, accounting for 1.5%. There were three patients with organ failure, including one with multiple organ failure and two subjects with only respiratory failure. There was no difference in the rate of systemic complications between the two groups.

Table 3. Coagulation disorder characteristics of children with acute pancreatitis

Classification		n	%
Blood clotting condition	Hypercoagulability	43	64.2
	Mixed hypercoagulability	24	35.8
Blood fibrinolysis	Yes	19	28.4
	No	48	71.6
DIC	High (≥ 5 points)	17	25.4
	Low (< 5 points)	50	74.6

Hypercoagulable disorder accounted for the highest rate (64.2%), mixed hypercoagulability accounted for 35.8%, and no patient had isolated hypocoagulable disorder. Thrombolysis was detected only in 19/67 (28.4%) cases, and 17 patients (25.4%) had DIC ≥ 5 points.

Table 4. Factors related to coagulation disorders in acute pancreatitis children

Characteristics		Coagulation disorders		No coagulation disorders		OR (95% CI)
		n	%	n	%	
Gender	Boy	37	69.8	16	30.2	0.998 (0.42 - 2.40)
	Girl	30	69.8	13	30.2	1
Covid infection	Yes	19	61.3	12	38.7	1.78 (0.72 - 4.43)
	No	48	73.8	17	26.2	1
Hyperlipidemia	Yes	13	100	0	0	**1.54 (1.31 - 1.80)**
	No	54	65.1	29	34.9	1
Pancreatic necrosis	Yes	7	100	0	0	**1.48 (1.28 - 1.71)**
	No	60	67.4	29	32.6	1
Free intra-abdominal fluid	Yes	46	92.0	4	8	0.073 (0.02 - 0.24)
	No	21	45.7	25	54.3	1
Peripancreatic fluid collections	Yes	39	95.1	2	4.9	0.053 (0.012 - 0.24)
	No	28	50.9	27	49.1	1

There was a relationship between hyperlipidemia and pancreatic necrosis with coagulopathy in children with acute pancreatitis. The likelihood of coagulopathy in the group with hyperlipidemia was 1.54 times higher than in the group with normal blood lipid level. When there was a complication of pancreatic necrosis, pediatric patients have a 1.48 times higher risk of coagulopathy. Other factors such as gender, covid infection, free intra-abdominal fluid, and peripancreatic fluid accumulation did not show any association with the status of coagulopathy in pediatric patients with acute pancreatitis.

IV. DISCUSSION

Of the 96 patients with acute pancreatitis who met the criteria for participating in the study, 69.8% had abnormalities in at least one of the coagulation test parameters. The average age of the group with acute pancreatitis and coagulation disorders was 6.1 ± 3.2 years, similar to the results from Chu Thi Phuong Mai et al. (6.5 ± 2.5 years).[7] Prevalence of boys having coagulation disorders was higher than girls, with no significant difference. The mean duration of treatment in the group of acute pancreatitis with coagulopathy was higher than the group without coagulopathy with $p < 0.001$. In general, the length of the treatment period depends on many factors, such as the cause of acute pancreatitis, the complications of the disease, and the response to each patient's treatment. This study also showed no difference in the treatment outcome between the group of acute pancreatitis with and without coagulopathy, with no patient death.

The clinical symptoms in the gastrointestinal tract of patients with coagulopathy were very diverse. Some of the symptoms at the onset were more prominent in this group, including abdominal pain (92.5%), vomiting (79.1%), abdominal distension (61.2%), and nausea (52.2%). This result is similar to some research focusing on the clinical characteristics of children with acute pancreatitis.[7,8] We found that the rate of acute pancreatitis with complications of organ failure was 3/96 patients (3.1%), and all of these cases belonged to the acute pancreatitis group with coagulopathy. The clinical manifestations of coagulation disorders was rare, with hemorrhage and thrombosis rates at only 3.1%. Hemorrhage was only seen in 1 case with moderate subcutaneous bleeding, and no significant bleeding cases were reported. Meanwhile, only one child with splenic venous thromboembolism complication was detected. Our study showed a lower rate of thrombosis complications than many other studies in the adult population.[9,10] This difference may be due to the differences in subjects, sample sizes, or the severity of pancreatitis populations. Among the local complications of acute pancreatitis, splanchnic venous thrombosis is not common. Still, it can lead to many serious consequences, such as gastrointestinal bleeding, ischemia of the small intestine, portal hypertension, and liver failure.[9] Data on splenic venous thromboembolism complications in children with acute pancreatitis were not sufficiently collected and mainly in the form of case reports. At the same time, studies in adults indicate that the splenic vein is the most common site of thrombosis (55.3%).[9] Usually, the splenic vein passes posteriorly to the tail and body of the pancreas. It is anatomically closest to the pancreas, which is easily affected by inflammatory pancreatic tissue, inflammation, and peripancreatic fluid accumulation. Many previous studies have suggested that the symptoms of splenic venous thromboembolism are silent and often overlap with the symptoms of acute pancreatitis, so they are often incidentally discovered when performing imaging tests to diagnose and

evaluate the severity level of acute pancreatitis. The patient in our study also accidentally detected splenic venous thromboembolism through computed tomography of the abdomen without any suggestive clinical symptoms or causing any complications.

Normally, in a healthy body, many mechanisms always exist to regulate the coagulation process. In acute pancreatitis, proinflammatory cytokines are released into the circulatory system causing activation of neutrophils and monocytes to focus on the injury site and activate endothelial cells to express tissue factor, thereby initiating the coagulation pathway, mainly through overactivation of coagulation factors, impaired anticoagulation, and impaired fibrinolysis.[2] These reactions lead to a hypercoagulable state in the early stages, overactivation causing microvascular formation, especially DIC causing multi-organ failure.[2] Simultaneously, increased platelet activation and coagulation factor consumption eventually lead to hypocoagulability, which can cause severe bleeding complications.[2] Our study showed that hypercoagulable disorder accounted for the highest rate (64.2%), followed by mixed hypercoagulable disorder (35.8%), and no patient was recorded with isolated hypocoagulable disorder. The results on the status of coagulopathy in this study can be explained by the fact that the patients in our study were admitted to the hospital at an early stage when the thrombocytopenia was mainly in the hypercoagulable phase, while the hypocoagulable disorder was commonly found in the late stages of the disease. The study also acknowledged 19 cases (28.4%) with fibrinolysis and DIC in 17/67 (25.4%) patients. The state of hypercoagulability and DIC are related to the severity and poor prognosis of acute pancreatitis, which is one of the mechanisms involved in the formation of microvascular thrombosis and organ failure. The case of splenic vein thrombosis in our study also had a high DIC score (6 points). Still, more studies with larger sample sizes are needed to find the relationship between them as well as the threshold of the DIC score to predict the risk of the formation of splanchnic venous thrombosis in children with acute pancreatitis.

The results of our analysis indicate that the occurrence of hyperlipidemia and pancreatic necrosis is the increased risk of coagulation disorder in children with acute pancreatitis. Hyperlipidemia is an elevation of cholesterol or triglycerides or both. Pathophysiologically, through tissue factor release and expression on circulating monocytes, hyperlipidemia contributes to the formation of atherosclerosis and venous thromboembolism. Our study showed that the risk of coagulopathy in pediatric patients with acute pancreatitis was 1.54 (95% CI: 1.31 - 1.80) times higher than in the non-hyperlipidemic group. Many studies have shown that pancreatic necrosis is related to the pathogenesis of venous thromboembolism in patients with acute pancreatitis. Necrosis induces a local inflammatory response, directly affecting adjacent blood vessels, causing vasomotor dysfunction, decreased capillary perfusion, and increased risk of thrombus formation.[9] Ding showed that necrosis of the body and tail of the pancreas increased the splanchnic vein thrombosis by 6.43 times and 8.5 times, respectively.[10] Our results indicated that pancreatic necrosis was a factor risk of coagulopathy with OR = 1.48 (95% CI: 1.28 - 1.71). However, we only studied the association between pancreatic necrosis and coagulopathy in general; thus, the relationship with the specific manifestations of coagulopathy must be further evaluated.

V. CONCLUSION

Coagulopathy is a common manifestation in children with acute pancreatitis, but it is difficult to recognize based on clinical manifestations. The factors related to coagulopathy in children with AP have been identified as hyperlipidemia and pancreatic necrosis. Routine coagulation testing, as well as identification of related factors for all children with acute pancreatitis, is necessary for early detection of coagulation disorders, which leads to timely monitoring and treatment.

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