

Surgical complications in children with IgA vasculitis: clinical analysis of 28 cases.

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Keywords: intussusception; intestinal perforation; Henoch-Schönlein purpura; enterectomy; enterostomy; D-dimer; C-reactive protein.

Abstract. Intussusception and intestinal perforation are surgical severe complications in children with IgA vasculitis (IgAV). Early diagnosis and timely appropriate surgical intervention can reduce damage to the children. We analyzed retrospectively the clinical characteristics, auxiliary examinations, diagnosis, treatment, and prognosis of 28 children with IgAV accompanied by surgical complications (including intussusception in 21 patients and intestinal perforation in seven patients) who were admitted to the Beijing Children's Hospital of the Capital Medical University from May 2016 to December 2020. Within one year after the data was collected, the parents of the children were interviewed by telephone about their treatment. Increased peripheral leukocytes were observed in 60.7% of children. Serum C-reactive protein (CRP) and D-dimer were elevated in 53.3% and 75% of children, respectively. Gastrointestinal bleeding was identified in 39% of children. Of the children with intussusception, the symptoms subsided spontaneously in four children and after air enema in another four. Four children underwent laparotomy and manual reduction. Nine patients underwent enterectomy and anastomosis. Enterectomy and anastomosis were performed in the seven patients with intestinal perforation, two of whom underwent enterostomy concurrently. Increased inflammation indexes, elevated D-dimer, and persistent abdominal pain without relief may be risk factors for surgical complications in children with IgAV.

Complicaciones quirúrgicas en niños con vasculitis IgA: análisis clínico de 28 casos.

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Palabras clave: intususcepción; perforación intestinal; púrpura de Henoch-Schönlein; enterectomía; enterostomía; dímero D; proteína C-reactiva.

Resumen. La intususcepción y la perforación intestinal son complicaciones quirúrgicas graves en niños con vasculitis por IgA (IgAV). El diagnóstico temprano y la intervención quirúrgica adecuada y oportuna pueden reducir el daño de esta enfermedad a los niños. Analizamos retrospectivamente las características clínicas, exámenes auxiliares, diagnóstico, tratamiento y pronóstico de 28 niños con IgAV acompañada de complicaciones quirúrgicas (incluida intususcepción en 21 pacientes y perforación intestinal en siete pacientes) que ingresaron en el Hospital Infantil de Beijing de la Universidad Médica de la Capital, de mayo de 2016 a diciembre de 2020. Un año después de la recopilación de datos, los padres de los niños fueron entrevistados telefónicamente sobre su tratamiento. Se observó un aumento de leucocitos periféricos en el 60,7% de los niños. La proteína C reactiva (PCR) y el dímero D séricos estaban elevados en el 53,3% y el 75% de los niños, respectivamente. Se identificó hemorragia gastrointestinal en el 39% de los niños. De los niños con intususcepción, los síntomas desaparecieron espontáneamente en cuatro niños y después de un enema de aire en otros cuatro. Cuatro niños fueron sometidos a laparotomía y reducción manual. Nueve pacientes fueron sometidos a enterectomía y anastomosis. Se realizó enterectomía y anastomosis en los siete pacientes con perforación intestinal, dos de los cuales fueron sometidos a enterostomía al mismo tiempo. El aumento del índice de inflamación, el dímero D elevado y el dolor abdominal persistente sin alivio pueden ser factores de riesgo de complicaciones quirúrgicas en niños con IgAV.

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INTRODUCTION

IgA Vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is a systemic small vasculitis syndrome that usually occurs in children. In 1802, Heberden first described this syndrome. He reported a child with joint pain and subcutaneous edema, abdominal pain, vomiting, blood in the stool and blood in the urine, as well as “blood spots” on the skin of the legs ¹. Initially,

Schönlein used the term “rheumatic purpura” to describe the association between joint pain and purpuric skin lesions in children. In 1874, Henoch described the syndrome of purpura, severe abdominal cramps, and melena. Later, Henoch referred to nephritis as a complication of the syndrome ².

The disease can cause purpuric skin lesions and is accompanied by various symptoms, including gastrointestinal symptoms, arthritis, and nephritis. Approximately 50%

to 75% of IgAV children present with gastrointestinal symptoms, such as abdominal pain³ with various degrees, from mild abdominal pain to severe intestinal colic. Some children may have serious surgical complications, including intussusception, intestinal perforation, intestinal necrosis, intestinal obstruction, significant gastrointestinal bleeding, severe pancreatitis, and testicular torsion. Delayed management and surgical intervention are associated with serious consequences and even death. We should carefully watch for surgical complications in children with severe abdominal pain and gastrointestinal bleeding. Complete examinations should be performed promptly to identify early complications, such as intussusception and intestinal perforation. Appropriate and timely treatment should be given accordingly. There are many reports on the use of corticosteroids and immunosuppressive drugs¹. These specific treatments are still controversial, and their efficacy remains to be evaluated. If the complications are severe, including severe gastrointestinal complications or proliferative glomerulonephritis, steroids or/and immunosuppressive drugs may be needed, including coledicine, dapson, montelukast, corticosteroids and azathioprine and other drugs⁴⁻⁶.

There have been relatively few clinical and epidemiological studies on childhood HSP in the past few years. To investigate this syndrome further, we retrospectively analyzed the clinical data of 28 children with intussusception or intestinal perforation among 7374 children with IgAV.

METHODS

From May 2016 to May 2020, 7374 children with IgAV were treated in the Department of Traditional Chinese Medicine, Beijing Children's Hospital, Capital Medical University. Surgical complications were reported in 28 children, including intussusception in 21 children and intestinal perforation in seven children. We retrospectively

analyzed the clinical characteristics, auxiliary examinations, diagnosis, treatment, and prognosis of all 28 children with IgAV. All data were collected from our Hospital's electronic medical record system.

Inclusion criteria

Patients with primary cutaneous vasculitis were classified as HSP or allergic vasculitis², according to the American College of Rheumatology (ACR) standards and the standards proposed by Michel *et al.* If the patient met the following three or more criteria, the patients were classified as HSP: 1) palpable purpura, 2) intestinal colic, 3) gastrointestinal bleeding, 4) hematuria (macroscopic or microscopic hematuria), 5) disease onset age ≤ 20 years, and 6) there was no history of drug treatment before the onset of vasculitis. Patients who met less than three criteria were classified as allergic vasculitis. In addition, if children were diagnosed with primary skin vasculitis or other diseases, such as connective tissue diseases and infections, especially meningitis⁷, they were excluded from the study. Because electronic medical records have only been used recently in our Hospital, only no more than three years of medical records were collected. The incidence of IgA vasculitis with surgical complications is not high, so only 28 cases were collected. A pre-existing anatomical factor as the starting point of the invagination, an accidental finding, and where the intussusception was spotted in such cases as to be taken as criteria for inclusion or exclusion.

Treatment methods

Surgical treatment: Of the 21 children with intussusception, the symptoms subsided spontaneously in four children and after air enema in four. Four children underwent laparotomy and manual reduction. Nine patients underwent enterectomy and anastomosis due to intestinal necrosis (one of them underwent enterostomy). Enterectomy and anastomosis were performed in the seven patients with intestinal perforation

(two of them underwent enterostomy concurrently).

Conservative treatment methods: According to the specific conditions of the children, the children were treated with fasting, gastrointestinal decompression, enteral or parenteral nutrition support, glucocorticoids, proton pump inhibitors, or gamma globulin, as needed.

Follow up

During the follow-up of all 28 children, three children had adhesive intestinal obstruction and underwent secondary surgery. Four children had multiple hospitalizations due to IgAV nephritis, and one child was readmitted due to abdominal pain.

Statistical analysis

The data are expressed as mean \pm standard deviation. The differences between the groups were analyzed using the chi-square test. $P < 0.05$ was considered statistically significant. All statistical analysis is performed using SPSS software (SPSS 19, IBM, USA).

RESULTS

General data

Twenty-eight of the 7,374 children with IgAV were accompanied by surgical complications, a rate of 0.38%. Twenty-one children had intussusception, and seven children had intestinal perforation. Of the 28 children, 10 were males and 18 were females. The age at onset ranged from 3 to 13 years (mean age: 7.2 years). The time from onset of purpura to occurrence of surgical complications ranged from 1 to 37 days (mean: 11 days), and the time from onset of abdominal pain to occurrence of surgical complications ranged from 1 to 40 days (mean: 9.8 days). Of these patients, 6 (6/28) children complained of abdominal pain before purpura appeared.

Clinical manifestations

All 28 children had symptoms of skin purpura. Seven children (7/28) had joint

swelling and pain, 11 (11/28) had gastrointestinal bleeding, and five (5/28) had IgAV nephritis (two cases with nephrotic syndrome and three cases with hematuria and proteinuria). All patients presented with apparent abdominal pain. Tenderness and rebound tenderness were noted on abdominal examination. An abdominal mass was palpated in four patients. The severity of the complications in patients was different, and four patients developed shock (hemorrhagic shock in one patient and septic shock in three patients). Convulsions occurred in two children (due to IgAV involving the cerebrovascular system). Three patients were complicated with pneumonia. After surgery, venous thrombosis occurred in three patients, renal dysfunction in one patient, pancreatic damage in one patient, thrombocytopenia in one patient, and coagulation disorders in one patient.

Auxiliary examination

A routine blood count showed increased leukocyte count in 17 children (17/28), with the highest value being $33.11 \times 10^9/L$ (normal range: $4-10 \times 10^9/L$). Elevated CRP was noted in 15 children (15/28), with the highest value being $> 160 \text{ mg/L}$ (average value $< 8 \text{ mg/L}$). Elevated D-dimer was noted in 21 children (21/28), with the highest value being 7.565 mg/L (normal limits: $0-0.243 \text{ mg/L}$). Four children tested positive in the ^{13}C -urea breath test. Serum influenza B virus IgM was positive in six children. Serum influenza A virus IgM was positive in two children. Serum mycoplasma pneumoniae IgM was positive in two children. According to abdominal B-mode ultrasonography or surgical exploration in some patients, 12 children were diagnosed with ileo-ileal intussusception, six children with ileo-colonic intussusception, two children with jejunal-jejunal intussusception, and one child with colon-colonic intussusception. Of the seven children with intestinal perforations, six were diagnosed with ileal perforation (including a child accompanied by colonic perforation) and a child with jejunal perforation.

DISCUSSION

IgAV is a common small-blood-vessel allergic disease occurring during childhood; it is most common in children aged three to eight years⁸, with a predominance in males. Skin purpura is most commonly accompanied by digestive tract, joint, or kidney lesions. Abdominal symptoms are reported in 50% to 75% of IgAV children, including gastrointestinal bleeding, gastric ulcers, pancreatitis, cystic effusion, and protein-losing enteropathy. Some rare surgical complications include intussusception, intestinal obstruction, intestinal fistula, and intestinal perforation^{3,9}.

Intussusception is the most common condition for surgery in IgAV children, with an incidence of 3% to 4%¹⁰. Intestinal perforation is the second-leading condition for surgery, with an incidence of approximately 0.38%¹¹. In the past three years, we have treated 7,374 patients with IgAV; surgical complications were reported in 28 patients. The incidence of intussusception was 0.28%, and the incidence of intestinal perforations was 0.09%. Due to our Hospital's late use of electronic medical records, no more than three years of case data have been counted. If the statistical years were longer, the data may be more meaningful. The pathogenesis of intussusception may be due to the aseptic inflammation of small blood vessels in the intestinal wall, which increases the permeability of the intestinal wall blood vessels^{10,12} to result in extravasation of blood components and segmental bleeding under the serosa and mucosa. These lead to uneven peristaltic movement, local slow peristalsis, spasms of the intestinal loop, or even intussusception¹³. As the disease progresses, tissue hypoxia and hypoperfusion may occur. Intestinal wall edema, ischemia, and hypoxia lead to intestinal necrosis and even intestinal perforation¹⁴. In the acute phase of IgAV, increased blood viscosity results in slow local blood flow and exacerbates intestinal ischemia and hypoxia. The circulating D-dimer level in children with IgAV is significant-

ly increased¹⁵. This reflects the presence of hypercoagulable states and the formation of thrombi. Another study¹⁶ found that IgAV caused a significant increase in serum CRP in children with abdominal surgical complications, suggesting that the occurrence of this complication may be closely related to infectious factors. Furthermore, serum CRP level has been positively correlated with the occurrence of these complications. This further indicates that infectious factors play an essential role in the occurrence of surgical complications. We summarized the clinical data of all 28 children in this study and found that the average time from the onset of abdominal pain to the first surgical complication was 9.8 days, and the longest time was 40 days. Increased peripheral leukocyte count was observed in 60.7% of children. Serum CRP and D-dimer levels were elevated in 53.3% and 75% of children, respectively. Gastrointestinal bleeding was identified in 39%. Increased inflammation index, elevated D-dimer, and persistent abdominal pain without relief may be risk factors for surgical complications in children with IgAV. For this child population, we should carefully watch for surgical complications. Early and precise diagnosis and timely, appropriate treatment can reduce the harm to these children.

Intussusception in IgAV patients usually originates from the ileum (90%) or jejunum (7%)¹⁷. The common sites of intussusception are ileo-ileal (51.4%), ileo-colonic (38.6%), and jejunal-jejunal (7.0%). In IgAV, colo-colonic intussusception is extremely rare, with only a few cases reported¹⁶. The most common site of intestinal perforation is the small intestine, especially the ileum, followed by the jejunum. This may be due to the intestinal wall swelling in the small intestine in IgAV patients. Children with IgAV also often have infection, which can enlarge the aggregated lymphoid nodules in the ileum. Therefore, the local intestinal wall thickens and even protrudes into the intestinal lumen to form a starting point of intussusception¹⁸. Among the children with

intussusception in this study, ileo-ileal intussusception, ileum-colonic intussusception, and jejunal-jejunal intussusception made up 57%, 28%, and 9.5% of all intussusceptions, respectively. Colo-colonic intussusception was seen in one patient. Of the seven children with intestinal perforation, six had ileal perforation, and one had jejunal perforation. The incidence of intestinal perforation is basically consistent with that in the literature.

Some researchers have suggested¹⁹ that air enema is the best reduction treatment for IgAV-related early intussusception. Air enema is minimally traumatic to children and can be done more than once. It is difficult to differentiate the abdominal pain caused by IgAV from the abdominal pain caused by complicated intussusception in IgAV because of certain similarities in the symptoms. Intussusception that occurs based on intestinal bleeding and edema is associated with rapid progression and intestinal necrosis. On the other hand, ileo-ileal intussusception is the most common kind, in which the failure rate and recurrence rate of air enema reduction is higher. This study relieved intussusception only in four children after air enema.

Children with IgAV-related surgical conditions may develop serious and even life-threatening complications. In this study, shock was reported in four children (hemorrhagic shock in one patient and septic shock in three patients), postoperative venous thrombosis in three patients, renal insufficiency in one patient, coagulation disorders in one patient, and adhesion intestinal obstruction in three patients, which required secondary surgery later. Therefore, we should improve our understanding of IgAV-related surgical complications to make early diagnoses and provide the appropriate surgical intervention.

The use of glucocorticoids for the treatment of IgAV has been controversial. Some researchers have suggested that early use of glucocorticoids can significantly relieve abdominal pain and reduce the risk of kidney disease²⁰. It can reduce the incidence²¹ or prevent intussusception²². Other research-

ers disagree^{10,23}. The use of glucocorticoids in patients with IgAV complicated with intussusception may mask the symptoms of intestinal perforation or aggravate the intussusception²⁴. Foreign studies have reported that IgAV-related intestinal perforation usually occurs two weeks after the application of glucocorticoids⁶. In this study, all 21 children with intussusception were treated with glucocorticoids, and some were treated with gamma globulin. The children's abdominal pain and purpura were alleviated. Of the seven children with intestinal perforation in this study, four had been taking glucocorticoids for more than 20 days, and three of them developed severe infections with septic shock. Therefore, the dosage and timing of glucocorticoids need to be further explored. However, it draws attention that from May 2016 to 2020, there is a registry of patients in the pediatric population that are diagnosed with IgA vasculitis (7,374 children), and none of the reports state that the diagnosis was confirmed through biopsies of white organs. There are a fair amount of cases (it is because the Hospital is a reference area, or the data collected is national or local); they may also have other pathologies that could be presented through a similar clinical picture, which would explain the large population reported. The risk-benefit of a steroid treatment prior to the appearance of surgical complications cannot be assessed in this work.

Due to the limited study funding and time, the deficiency of this study is the failure to collect the characteristics of each case (onset, relevant laboratory tests, treatment time before symptoms and signs, laparotomy results, air enema treatment, etc.). Moreover, a range of examinations evaluate the inflammatory response (CB, PCR, Dimer D), and the predictive value and prognostic value cannot be established with this work. Our team will conduct the study in the future. Meanwhile, a better collection of clinical, laboratory, and imaging data is needed to establish prognostic value in patients with said pathology.

Table 1
Clinical data of the 28 children with Henoch-Schönlein purpura accompanied by surgical complications.

Number	Joint swelling and pain	Gastrointestinal bleeding	Kidney damage	Surgical complications	Site	Surgical treatments	Other comorbidities	Reason for rehospitalization
1		+	+	Intussusception	Ileo-ileal	Air enema		IgAV nephritis
2	+	+		Intussusception	Ileo-ileal	Enterectomy and anastomosis		
3		+	+	Intussusception	Ileum-colon	Open laparotomy and manual reduction	Venous thrombosis	
4				Intussusception	Ileo-ileal	N/A	pneumonia	
5		+	+	Intussusception	Ileo-ileal	Enterectomy and anastomosis	Hemorrhagic shock, Pneumonia, Coagulation disorders	IgAV nephritis
6	+			Intussusception	Ileo-ileal	Open laparotomy and manual reduction		
7				Intussusception	Jejunum-jejunum	N/A		
8		+		Intussusception	Ileo-ileal	Enterectomy and anastomosis		Intestinal obstruction
9		+		Intussusception	Ileo-ileal	N/A		IgAV nephritis
10		+		Intussusception	Ileum-colon	Air enema		
11				Intussusception	Ileo-ileal	Enterectomy and anastomosis		
12				Intussusception	Ileo-ileal	Open laparotomy and manual reduction		
13	+			Intussusception	Ileum-colon	Enterectomy and anastomosis		
14				Intussusception	Ileum-colon	Open laparotomy and manual reduction		
15		+		Intussusception	Ileo-ileal	Enterectomy and anastomosis		
16	+			Intussusception	Ileum-colon	Air enema		IgAV
17				Intussusception	Jejunum-jejunal	Enterectomy and anastomosis		
18	+		+	Intussusception	Colonocolonic	Air enema	Pneumonia	
19		+		Intussusception	Ileo-ileal	Enterectomy and anastomosis	Pancreatic damage	Intestinal obstruction
20				Intussusception	Ileo-ileal	Enterectomy and anastomosis + enterostomy		
21				Intussusception	Ileum-colon	N/A		
22				Intestinal perforation	Ileum	Enterectomy and anastomosis		Intestinal obstruction
23				Intestinal perforation	Ileum, colon	Enterectomy and anastomosis + enterostomy	Septic shock, renal insufficiency, Convulsions	
24				Intestinal perforation	Ileum	Enterectomy and anastomosis	septic shock, Convulsions, Venous thrombosis	
25		+		Intestinal perforation	jejunum	Enterectomy and anastomosis	Septic shock, Venous thrombosis, Thrombocytopenia	
26			+	Intestinal perforation	Ileum	Enterectomy and anastomosis		
27				Intestinal perforation	Ileum	Enterectomy and anastomosis		
28			+	Intestinal perforation	Ileum	Enterectomy and anastomosis + enterostomy		IgAV nephritis

As a conclusion, intussusception and intestinal perforation are serious surgical complications of IgAV. Clinicians should make an effort to understand IgAV-related surgical complications. Once specific symptoms are present, including increased inflammation index, elevated D-dimer, persistent abdominal pain without relief, and digestive tract hemorrhage or previously existing intestinal malformations, we should observe for surgical complications and make a clear diagnosis as soon as possible. Appropriate and timely surgical intervention can avoid delayed treatment and reduce mortality.

Ethics approval and consent to participate

All procedures performed in studies involving human participants followed the ethical standards of the Independent Ethics Committee for Clinical Research and Animal Trials of the Beijing Children's Hospital, Capital Medical University, and the National Center for Children's Health. Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors state that no financial, personal, or professional conflicts of interest may hinder this work.

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Authors' contributions

JM, JH, XFZ, and XM performed material preparation, data collection, and analysis. JM and YS wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

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