

REVIEW ARTICLE

The cause of abdominal purpura in children and the advances in pathogenesis

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Abstract: This paper analyzes the imaging and gastrointestinal function of patients with abdominal purpura by searching domestic (China) and foreign literature, combined with clinical experience, and explores the possible characteristics of the disease of the children's abdominal from the three perspectives of *Helicobacter pylori* infection, parasitic infection and food-intolerance type of purpura, as well as the development of closely related factors and new ideas for the clinical treatment of abdominal purpura children and for avoiding exposure to risk factors in order to reduce the recurrence rate.

Keywords: abdominal purpura; related factors; infection; food intolerance

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51%–74% of patients with Henoch-Schonlein purpura (HSP) may present with gastrointestinal symptoms, and severe symptoms such as intussusception, intestinal necrosis, intestinal perforation and other critical complications may occur^[1].

Previous studies suggest that abdominal purpura is a pathologically IgA-mediated systemic microvascular inflammation^[2]; vasculitis caused by acute visceral smooth muscle ischemic injury leading to visceral smooth muscle movement disorder may lead to abdominal purpura GI tract performance mechanism. However, in recent years, some research have shown that the etiology and pathogenesis of abdominal purpura is more complex, and the research are summarized as follows:

1. Progress of imaging in abdominal purpura

Gastrointestinal endoscopy: With digestive endoscopy becoming more popular for pediatric patients, more and more abdominal purpura patients undergo upper gastrointestinal endoscopy. Endoscopy can reveal that abdominal purpura is caused by gastrointestinal mucosal damage occurring in the stomach and the second (descending) part of the duodenum and the terminal ileum^[3,4], with microscopic manifestations of diffuse mucosal congestion and edema, extensive erosion, ulcers, bleeding, and mucosal lesions similar to the skin purpura; the typical presentation is different degrees of purple-red mucosa rash, and mucosa lesions can be normal^[5–7]. In children with abdominal hypersensitivity purpura children, gastrointestinal vascular inflammation is caused by increased vascular permeability, resulting in cell fluid extravasation, interstitial edema, intestinal wall thickening, swelling, peristalsis disorders, and gastrointestinal mucosal damage, resulting in symptoms of abdominal pain^[3,8]. So, clinician's attention should be on the treatment of gastrointestinal mucosal injury.

Ultrasound: High-frequency ultrasound examination of HSP abdominal purpura reveals acute intestinal swelling (intestinal thickening) and flow changes in small blood vessel of the intestinal wall after the acute phase disappeared. The above signs have a strong specificity^[9,10] and sensitivity (50%~100%),^[11] and are worthy of attention.

2. Intestinal barrier function is impaired

The intestine does not only have digestion and absorption functions, but also has an important barrier function: the body plays a protective role in avoiding intestinal harmful substances from entering into the body. At present, the evaluation of intestinal mucosal barrier function index is still controversial, but the more recognized are plasma diamine oxidase (DAO) and D-lactic acid determination. DAO is a highly active intracellular enzyme in human and all mammalian intestinal mucosal epithelial cells with the highest jejunum and ileum activity. DAO exists in the upper layer of small intestinal mucosa villi and can reflect the structure and function of the small intestine, and the increase in plasma DAO suggests damage to the intestinal barrier^[12].

Gao Xiaolin, *et al* shows the results of comparison of plasma DAO, D-lactic acid and endotoxin in children with HSP indicate that plasma DAO, D-lactic acid and endotoxin cannot only reflect mucosal damage and function change, but it can also reflect the mucosal damage after the repair process. This is obvious in HSP children with intestinal mucosal barrier dysfunction and injury and in children with HSP gastrointestinal symptoms^[13].

3. Intestinal microecological changes of abdominal purpura

The ratio of Bifidobacterium and Enterobacteriaceae in the intestine (B/E) was first proposed by Dutch scholar van der Waaij and colleagues^[14] as an indicator of the resistance of intestinal microbial colonization. The results showed that the content of lactobacilli and bifidobacteria in children with abdominal purpura^[15] was significantly lower than that in healthy children, and was lower than that in children without gastrointestinal symptoms. However, there was no statistically significant difference between lactobacilli and bifidobacteria in intestinal tracts of healthy children and those with gastrointestinal symptoms. Intestinal flora imbalance weakens the role of biological barrier, and promotes the development of HSP digestive tract symptoms.

4. Infection of *Helicobacter pylori*

In recent years, the study of abdominal purpura complicated with *Helicobacter pylori* (HP) infection has gradually increased. In 1995, Reinauer *et al.* first reported that, in a 21-year-old female HSP patients with HP infection-related chronic atrophic gastritis, the skin purpura's clinical symptoms disappeared after HP eradication therapy^[16]. Wang and others^[17] studied 36 cases of abdominal purpura in children, and 16 of 32 cases of non-abdominal HSP, who underwent gastric and duodenal endoscopy and rapid urease test. Of the 36 patients with gastrointestinal manifestations, HP-positive rate was 58.3%, (21/36) and in 16 cases of relapsed patients, HP-positive rate was 81.3% (13/16), and the authors concluded that there is an association of incidence of abdominal HSP and recurrent episodes with HP infection. Zhang and others^[18] studied 23 cases of abdominal hypersensitivity purpura in children with endoscopy and *Helicobacter pylori* detection, and found that gastric mucosal lesions detection rate was 100% and blood HP-positive rate was 56.52%. The detection rate of HP in the biopsy tissue was 69.57%, which indicated that HP might be the main cause of recurrent episodes of abdominal HSP.

Hu^[19] reported that HP infection after gastrointestinal mucosa weakens the gastrointestinal mucosal barrier function, which increases the body and the digestive tract allergens' (food, drugs, pathogens, including HP, *etc.*) contact opportunities to enlarge the degree of allergic reactions and then increases the occurrence of HSP rate. HP virulence factor CagA, vacuolating cytotoxin A (VacA), heat shock protein 60 (Hsp60) and other pathogenic factors may stimulate the body to produce abnormal immune response^[20]. In 2012, Xiong and others^[21] conducted a meta-analysis study on Chinese children and the association between with HP infection and allergic purpura, and found the necessity for the screening of *Helicobacter pylori* infection especially in children with abdominal purpura. The HP eradication therapy can reduce the recurrence of children with allergic purpura. However, there is a need of further mechanism and clinical studies in different populations and regions to corroborate the eradication therapy of *Helicobacter pylori* associated with HSP children and its effects.

According to the above data analysis, HP infection may cause or aggravate abdominal purpura and other reasons. It is not clear whether the two are causative factors or synergies. To confirm the relationship between the two, further studies are needed.

5. Parasite infection

With the improvement of people's living standard and the change of diet concepts, more and more people began to pay attention to the health problems of diet, so modern clinical parasitic diseases have been significantly reduced compared to the last century^[22]. However, soil-borne nematode (roundworm, whipworm, hookworm, pinworm, *etc.*) infection has increased in trend. Soil-borne nematode infection is a common in developing countries in the tropical, subtropical and temperate regions. WHO defines it as a neglected tropical disease and is one of the most common public health problems^[23], especially in rural areas, as it is a parasitic disease that causes serious harm to the people's health, affecting the socio-economic development. In addition, some people do not pay attention to the zoonotic parasites, such as toxoplasmosis, cryptosporidiosis and other AIDS-related protozoa disease, that in some developed countries in Europe and the United States cases are beginning to surge^[24,25].

Intestinal parasite infection cases caused by abdominal purpura have been reported in recent years. In 2014, Wang and Tan^[26] reported two cases of recurrent seizures of patients with Henoch-Schonlein purpura (one case associated with abdominal discomfort) in the anti-parasite treatment before a variety of drug treatment. Rash had repeatedly occurred. In 2013, Tutanç *et al.*^[27] had a case of steroid treatment of a child with purpura with 30 months of follow-up, and found that the recurrence of blastocysts (*blastocystis hominis*) was detected in the fecal analysis of the patient, in order to propose the relation between human embryo protozoa and abdomen type purpura.

In recent years, the incidence of soil-borne nematodes in China is still high: in 2005, the Ministry of Health announced a major parasitic diseases survey of the national population^[28]. The results: the national soil-borne nematode infection rate was 19.56%, and the estimated number of infected cases was 129 million. Between 2006 and 2010, 22 national surveillance sites were set up. The roundworm, whipworm and hookworm eggs were examined by modified Kato thick smear (three tests on one fecal). Transparent tape cleaning method would detect pinworm eggs. The 2006–2010 results showed that the infection rate of soil-borne nematode was 37.8%, 29.55%, 25.93%, 31.25% and 24.42%, respectively. The results showed that the rate of soil-borne nematode was 20.88%, 18.93%, 16.59%, 13.30% and 11.25%, respectively ($R = 0.90$, $P < 0.05$); children and young adults were still the highly infected people^[29].

The study of parasitic sampling of many vegetables shows that edible vegetables are an important source for human infection of parasites: In 2004–2005, following the survey of Guangzhou area^[30], the survey of vegetables detected the human parasite eggs and the rate was 21.37%. Among the different survey sites, the detection rate at vegetable plantations was the highest, which was 36.47%. Between 2011–2012, Wang *et al.*^[31] studied 13 local Yangzhou varieties of 130 kinds of fresh vegetables for sampling, statistics of various types of eggs detection rate and a variety of vegetables detection rate, and the results showed that roundworm egg retrieval rate of 13.85%, the detection rate of whipworm was 3.08%, the detection rate of hookworm eggs was 1.53%, the total detection rate in vegetables reached 21.54%, and especially the detection rate in parsley was as high as 70%.

In recent years, in order to reduce the use of chemical fertilizers, the cultivation of vegetables generally used livestock stool or inadequately treated sludge as a crop fertilizer; when people directly come in contact with this soil, or when people eat the crops on which it is planted, the parasite infects^[32].

In addition, the stool parasite test method may not be correct, and is also a very common problem. In 2016, Fan^[33] examined parasite eggs in 1,088 cases of fecal samples by saturated saline floatation method, direct lens method, water precipitation method and saturated sodium citrate solution. The detection rate was significantly different between the methods (27.8%, 17.0%, 32.7%, 42.0%, respectively), especially for the detection rate of roundworm eggs (0%, 3.0%, 18.9%, 25.0%, respectively), and the reason is that the specific weight of untreated roundworm eggs is 1.210~1.230, the same as the proportion of saturated brine. In view of the lack of attention to the harmfulness of parasitic diseases, and even laboratory operators are lacking experience and laboratory process not standardized, and that the parasite test method is not correct, the possibility of false negative of the laboratory check is great.

Therefore, clinical work should pay attention to the belly purpura children for parasite-related checks, with the best selection being the modified Kato thick smear method, for suspected cases in time for deworming treatments.

6. Food intolerance

Food intolerance is associated with a variety of chronic diseases and can involve digestion, skin, nerves, cardiovascular and other systemic system, the most common of which is the digestive system^[34]. Gastrointestinal mucosal immune system is a variety of immune cells and immune factors together constituting a complex network system and the intestinal nervous system (ENS) interaction. Any change in one of the links will lead to a broken immune balance^[35]. Immune incompatibility may be one of the pathogenesis of food intolerance. In the highly antigenic colorectal environment, the intestinal mucosal immune system continuously interacts with food antigens from the outside and hosts normal flora and pathogenic microorganisms, and the gastrointestinal environment is dependent on immune tolerance and immune activation. In contrast to IgE-mediated rapid-onset food allergies, IgG-mediated food intolerance is a delayed response, often caused by a variety of food-specific IgG antibodies and food particles forming immune complexes which can cause multiple intestinal and systemic tissue inflammatory response. Food intolerance and gastroesophageal reflux, inflammatory bowel disease, irritable bowel syndrome and other diseases are closely related^[36–38].

Liu's study^[39] of clinical trials found that the positive rate of children with HSP abdominal purpura with food-specific IgG antibody was significantly higher than the healthy control group and simple allergy HSP group of children, mostly children with three or more food intolerance, suggesting that food intolerance plays an important role in the pathogenesis of abdominal HSP in children. It is confirmed that there is a significant correlation between food-specific IgG and HSP in children, and the treating the effect of intolerance of food can effectively improve the treatment of abdominal HSP.

In Li's study^[40] of children with abdominal purpura, the positive rate of IgG was 63.3% (19/30) and 94.4% (34/36) in the relapse group. The positive rate of the control group was only for 18.8% (6/32), suggesting that food intolerance is associated with the onset and recurrence of abdominal hypersensitivity purpura.

As the environment and diet change, the incidence of food intolerance increases year by year. Although the mechanism of food intolerance is not clear, its impact is obvious. The relationship between food intolerance and children with abdominal purpura is especially more complex. Therefore, it is necessary to continue to study the mechanism of food intolerance and its systemic complications in the digestive diseases, such as positioning, and further improve the diagnosis and treatment for patients in order to develop individualized, rational diet recommendations. Reducing the intolerance of food will continue to form a new immune complex in the body to avoid damage sustained by unsuitable food and can control the sustainable development of the disease, and then significantly improve the health and quality of life of children and reduce the recurrence rate of abdominal purpura.

Conclusion

It is difficult to make an early diagnosis for children with abdominal purpura in the skin before the onset of the disease because the clinical symptoms and signs can be easily confused with other abdominal pain. However, endoscopy and ultrasound findings are specific, and gastrointestinal lesions can be visually found, contributing to early diagnosis. Although this article describes the abdominal purpura associated with a variety of factors, there is still need to further explore the causes of abdominal purpura factors and mechanisms so that children with simple allergic purpura may avoid contact with these factors, and may remove the abdominal purpura in the children. Related risk factors can also guide the clinical treatment program to reduce abdominal recurrence rate of abdominal purpura, and then improve the prognosis.

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