Overview of the pathogenesis of Henoch–Schonlein purpura in children and the research progress on related mechanism of inflammatory cytokines

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ABSTRACT

Henoch-schonlein purpura (HSP) is a kind of systemic vasculitis that is common in childhood, and its pathogenesis is complicated and considered to have important relationship with lymphocytes, vascular endothelial cells and so on. The causes of this disease are complex and have not been clearly identified, but numerous studies have shown that inflammatory factors such as IL-1, IL-17 and TNF-α play an important role in the development of HSP.

1. Introduction

The Henoch-Schonlein purpura (HSP) is a common microvascular allergic hemorrhagic disease in childhood[1]. Before the onset, patients often have upper respiratory infection symptoms such as fever and cough, then the skin petechiae with symmetrical distribution and different sizes appear successively in the lower limb joints, around the hip and so on, and some patients have visible ecchymosis flake[2]. Henoch-Schonlein purpura in children mostly regresses spontaneously within a few days, but is easy to relapse. The clinical symptoms are changeable, and some patients have obvious abdominal pain, which is paroxysmal or persistent; or have joint pain; or have renal symptoms that are mainly proteinuria and hematuria[3]. Modern medicine believes that the disease has significant correlation with autoimmune disorders, and some of the allergic materials make the capillary show high permeability and high brittleness, which causes the hemorrhage and edema in subcutaneous tissue and organ[4]. The epidemiology, etiology and related inflammatory factors of HSP are summarized as follows.

2. Epidemiology

According to statistics, the number of HSP cases under the age of 10 accounts for about 90% of the total number of cases[5]. According to the results of Piram M and others[6], the annual incidence of children is about 3-26.7/100 000, and children younger than 5 are mainly affected. The incidence of HSP in male is higher than that in female, and the ratio is about 2:1; as for race, the incidence of HSP is the highest in the white race, the incidence in the yellow race is the second, and the incidence in the black is the lowest.
3. Etiology

3.1 Infection

The patients mostly have a history of infections before onset, common cases include respiratory infections such as children's cold, pharyngitis and tonsillitis, and some patients have intestinal, urinary tract, skin and other infections. CHANG Ke and others[1] conducted field investigation on the 150 children with Henoch-Schonlein purpura in pediatric outpatient and inpatient ward of Affiliated Hospital of Chengdu University of TCM, and the results showed that the children with history of infection before the onset accounted for about 37.3% of all children, and the proportion was the largest; FANG Qian and others[9] retrospectively analyzed the 695 HSP cases who were treated in Children's Hospital of Hebei Province between May 2010 and May 2012, and the results showed that 30.2% (210 cases) of the children had the history of upper respiratory tract infection before the onset, and the proportion was the largest. TANG Pu-run and others[9] analyzed the causes of 306 children with Henoch-Schonlein purpura in Pediatrics Department of the Second Affiliated Hospital of Guangzhou Medical University between 2004 and 2013, and the results showed that infection factors accounted for 54.9% (168 cases), and 34.9% (107 cases) were with mycoplasma pneumoniae infection. All the above results indicate that infection may be involved in the pathogenesis of HSP.

3.2 Food.

The childhood is in the growth and development stage of various organs, the immune system is not mature, and it is the high risk stage of food allergy. The study[10] shows food-borne factors, the inducing factors of HS include milk, egg, fish, shrimp, crabs, etc., and some can relapse due to these factors. The food intolerance rate in children with HSP is as high as 92.5%. After entering the body, the allergen damages the intestinal "steady-state" system, causes the immune cells to abnormally secrete cytokines, and leads to the symptoms such as breathing, digestion and skin.

3.3 Drugs

The drugs mainly include antibiotics, blood products, shots, biological agents, etc. The research results of Aktas and others[11] showed that one patient with acute granulocytic leukemia developed Henoch-Schonlein purpura during cytarabine treatment.

3.4 Others

Pollen, dust, snake worm toxin, etc., can all cause HSP.

4. Inflammatory factor effects

4.1 IL-17

Unlike Th1, Th2 and CD4 + CD25 + Treg cell subgroups, Th17 cells do not express IL-4 or INF- γ , but massively express the IL-17, which is composed of IL-17A and IL-17F dimer. IL-17 is involved in the body's inflammatory response or autoimmune response by secreting pro-inflammatory cytokines by itself or inducing macrophages, endothelial cells and others to massively secrete IL-1β , TNF- α , IL-8, MCP-1 and other chemokines[12]. IL-17 is highly expressed in patients with rheumatoid arthritis, asthma, multiple sclerosis, chronic lymphocytic thyroiditis, goodpasture syndrome and autoimmune hemolytic anemia and other autoimmune diseases. The mutually exclusive relationship between IL-17 and CD4 + CD25 + Treg specific transcription factor Foxp3 is an important factor to maintain the immune balance in the body. Many studies have shown that IL-17 expression increases in patients with HSP, and the expression of CD4 + CD25 + Treg specific transcription factor Foxp3 with immunosuppressive action decreases significantly, and it indicates that the imbalance between IL-17 and Foxp3 is an important factor that induces the cascade of HSP pro-inflammatory cytokines and chemokines, and then causes vasculitis[13]. FAN Qiuxia and others[14] adopted double antibody sandwich enzyme-linked immunosorbent assay method to determine the peripheral blood serum IL-17 concentration in 40 children with acute HSP and 30 healthy children with physical examination, and the results showed that serum IL-17 concentration in children with acute HSP was significantly higher than that in healthy children; the research results of LIU Ping and others[15] showed that IL-17 was highly expressed in children with HSP while the level of CD4+CD25+Treg decreased, indicating that the high expression of IL-17 caused by Th17/Treg balance disorder promotes the HSP attack to a certain extent.

4.2 TNF- α

Tumor necrosis factor (TNF) is mainly produced by activated macrophages, natural killer cells and T cells, the factor produced by macrophages is called TNF- α , and the lymphotoxin produced by T lymphocytes is called TNF- β . As a cytokine with various biological effects, TNF- α plays a dual role in immune regulation and its expression affects the stability of the immune system. Appropriate amount of TNF- α , as an important medium for immune regulation, can effectively improve the immune protection ability; High expression of TNF- α not only causes endothelial cell damage, but is also combined with the corresponding receptors on the cell membrane and enters into the cells to reduce the stability
of lysosome, make the enzymes enter into cell SAP, and lead to the damage of the cell integrity and the generation of inflammation. The type I and II allergic reactions in patients with HSP cause capillary endothelial cell damage and express a large number of TNF-α, leading to the cytolysis and apoptosis. In addition, TNF-α can be combined with lipopolysaccharide to act on platelet activating factors, damage the integrity of the glomerular vascular wall and aggravate the injury of HSP kidney disease. XING Jing and others[16] conducted a comparative analysis between 200 children with acute HSP and 20 healthy children, and the results showed that the TNF-α level in children with acute HSP was significantly higher than that in healthy children; the results of a number of studies[17,18] showed that the TNF-α level obviously increased in children with HSP, and the TNF-α expression levels were significantly different in the children with or without Henoch-Schonlein purpura nephritis, prompting that TNF-α is closely related to the onset of children with HSP, and the TNF-α expression can predict the progression of HSP.

4.3 CRP

C-reactive protein (CRP) is synthesized by the liver and normal concentration is 0.068-8.2 mg/L. When inflammation occurs in the body, CRP increases rapidly and reaches a peak within 48 h of early disease, and its concentration decreases with the improvement of the disease[19]. CRP, as an acute phase protein, can react with pneumococcal C polysaccharide to damage tissue and cells, and amplify the inflammatory reaction cascade. In the past, due to the lag in detection technology, the false positive rate and the false negative rate of CRP are higher, which seriously influence its application value in clinic. With the advancement of medical technology, CRP, as a marker to determine the severity of inflammatory response, has been gradually accepted in clinic. The research results of CAO Hong and others[20] showed that CRP in children with acute HSP was obviously higher than that in children with convalescent disease and healthy children, and there was no obvious difference in CRP expression between children with convalescent disease and healthy children, indicating that the immune system in children with acute HSP is in an imbalance state, and the inflammatory response is obvious. Study has shown that[21] IL-6 and TNF-α can induce the hepatocytes to massively release CRP, and CRP can further promote the mononuclear macrophages to release IL-6, TNF-α and so on, which triggers the immune imbalance in children with HSP.

4.4 IL-1

Interleukin-1 (IL-1) is the cytokine produced by macrophages during infection response, and its biological activity changes with the change of concentration. When the biological activity of IL-1 is low, it can promote the activation of antigen presenting cells and T cells so as to increase the production of antibodies and regulate immunity; when the biological activity of IL-1 is high, it can promote the synthesis of 2 globulin, fibrinogen, c-reactive protein and other acute phase proteins to cause fever and cachexia and exert endocrine effect. IL-1 is divided into IL-1α and IL-1β, IL-1β is composed of 159 amino acids, and IL-1β consists of 153 amino acids. Study showed[22] that IL-1β plays a key role in regulating renal tubular epithelial cell injury and interstitial fibrosis. The research results of GAO Tian-ji and others[23] showed that the expression of IL-1β significantly increased in children with HSP, and the concentration of IL-1β in HSP nephritis group was significantly higher than that in HSP nephritis group, showing that IL-1β is involved in the onset of HSP and HSP nephritis. The study results of FU Yan-hua and others[24] showed that the PLT count and IL-1β expression in children with acute HSP increased significantly, and the PLT count was positively correlated with serum IL-1β level, indicating that the increase of PLT count is associated with high expression of IL-1β.

4.5 IL-6

The molecular weight of interleukin-6 (IL-6) is between 21 ~ 30kd, it is produced by activated monocytes/macrophages, activated lymphocytes, endothelial cells and so on, and it can promote the massive proliferation of lymphocytes[25]. On the one hand, IL-6 stimulates B lymphocyte to synthesize and secrete a large number of IgE and IgA, and the generated immune complex deposits in the glomerular mesangial region, activates the complement and causes nephritis; on the other hand, it stimulates T cell activation and proliferation, directly causes abnormal hyperplasia of glomerular mesangial tissue, and leads to glomerular fibrosis[26]. The research of Shin JI and others[27] showed that the expression of IL-6 is significantly higher in the acute stage of children with HSP, and the expression of IL-6 in HSP nephritis was obviously higher than that in HSP nephritis group, indicating that IL-6 plays an important role in the occurrence and development of HSP and HSP nephritis. The research results[28,29] showed that the concentration of IL-6 significantly increased in the acute stage of children with HSP, and significantly decreased in the recovery stage, and the IL-6 concentration in HSP nephritis group was significantly higher than that in the non-nephritis group. The research results[30] showed that the IL-6 levels in HSP children with abdominal surgical complications on day 1, 3 and 5 after admission were significantly higher than those on day 3 and 5 after surgery and in those without surgery, and IL-6 levels on day 3 and 5 after surgical treatment were significantly lower than those in children without surgery, indicating that IL-6 has certain reference significance for illness judgment and treatment of the abdominal surgical complications in children with HSP.
4.6 TGF-β

Transforming growth factor-β (TGF-β) is the disome of two subunits with identical or similar structure and molecular weight 12.5kDa that are connected by disulfide bond, which can be divided into TGF-β 1, TGF-β 2 and TGF-β 3, and has the biological activities of regulating cell growth and differentiation. TGF-β plays a negative regulating role in maintaining the immune system by inhibiting or down-regulating Th1/Th2 function. The study results of YANG Hua-bin and others[31] showed that TGF-β can stimulate the body to secrete a large amount of IgA, and cause the massive accumulation of immune complexes and the generation of vasculitis. The excessive expression of TGF-β causes the abnormal proliferation of glomerular mesangial cells and the massive accumulation of extracellular matrix, accelerates glomerular sclerosis and causes renal tissue fibrosis. The research results of MASSIVE accumulation of extracellular matrix, accelerates glomerular abnormal proliferation of glomerular mesangial cells and the generation of vasculitis. The excessive expression of TGF-β shows that TGF-β 1 in children with HSP was significantly higher than that in healthy children, and it is speculated that TGF-β 1 is an important factor causing the incidence of HSP children.

5. Conclusion

With the continuous progress of scientific research, the pathogenesis of HSP in children has made great clinical progress, but there is no definitive conclusion yet. The common complication of HSP is HSP nephritis, which can lead to renal insufficiency without proper treatment. In clinic, glucocorticoids and antiallergic drugs are mostly adopted to treat children with HSP, but there is still important basis for the use of drugs. Inflammatory cytokines play an important role in the pathogenesis of HSP; some inflammatory factors significantly change with the change in the course of HSP, and it is still a hot spot in future clinical studies whether the expression of these inflammatory factors can be used to accurately diagnose and predict the condition of HSP, and even properly treat HSP.

References


