Review

CURRENT KNOWLEDGE ON THE PATHOGENIC MECHANISMS OF HENoch-SCHOENLEIN PURPURA IN CHILDREN

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ABSTRACT

The Schönlein-Henoch vasculitis is an IgA-mediated inflammation of small vessels. The main clinical manifestation is palpable purpura without thrombocytopenia, manifested by bilateral symmetrical distribution on both lower limbs, abdominal pain, often accompanied by blood in the stools, hematuria with / or without proteinuria.

Historically, the disease has been known since 1832. In Bulgaria, although that later Henoch-Schönlein purpura (HSP) aroused scientific interest, several publications focused on the pathogenic nature, clinical variations, and potential complications of the disease, as well as options for therapeutic intervention.

Modern knowledge about the etiology and pathogenesis of the disease has given new light, respectively a basis for early diagnosis, reduction of complications and recurrences, as well as the avoidance of polypragmatism.

It turned out that in HSP there are genetic factors and new aspects, binding until now accepted concept that there are no changes in the coagulation system. The role of factor XIII, as a prognostic indicator of the severity of clinical manifestations and von Willebrand factor (vWF), as a reliable index of the degree of vascular wall damage, has been demonstrated. Plasma imbalance in the Th1 / Th2 ratio was also found and a percentage of NK cells, respectively their immune function, were reduced.

This new knowledge about the pathogenic nature of HSP is the basis for a change in the concept of therapeutic behavior, which is aimed at the severity of the clinical course, and not only at the treatment of the disease, which is itself symptomatic.

Key words: Henoch-Schönlein purpura, Th1/Th2 imbalance, FcαRI, f.XIII, vWF

INTRODUCTION

The Henoch-Schönlein purpura is a vasculitis of the small vessels as a result of IgA-mediated inflammation. It is the most common acute systemic vasculitis in childhood, affecting mainly the skin, gastrointestinal tract, joints, and kidneys. The main clinical manifestation of HSP is purpura without thrombocytopenia, characterized by bilaterally symmetrically distributed palpable purpura on the both lower limbs, abdominal pain, arthralgia, blood in the stool, hematuria, and/or proteinuria. (1, 2)

Increased production of polymeric IgA by the mucosal immune system in response to a

mucosal antigen, such as bacteria, viruses, or fungi, is thought to be the major mechanism of HSP. In the acute phase of HSP, the concentrations of anti-inflammatory cytokines are increased, which causes endothelial damage. (3)

HSP is a disease of children between 3 and 10 years of age. The overall incidence in children is estimated at 3-26.7 cases per 100,000 (4, 5). Historically, the first description was made in 1832 from Schönlein in Berlin. Forty years later, Edward Henoch (6) described the association of gastrointestinal symptoms and a rash. There is an excellent description of Haberdern in 1801 and another one from Wilan-1808. (7, 8) At the turn of the 19th century, William Osler devoted many of his active years to the study of the disease and

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developed the concept that it was anaphylactoid purpura. (8) In 1947 Douglas Gairdner wrote a book about the HSP.

Although Schönlein and Henoch gave their names to the disease, other notable physicians had noticed it, even earlier. In Bulgaria, the interest of pediatricians in HSP is associated with several scientific reports. St. Dimitrov (9) makes the first generalized description of Schönlein-Henoch disease. The first monographic work was published in 1966 by Lilyana Basheva-Staneva. (10) She adopted the immune-allergic genesis of Schönlein-Henoch and concluded that it was hyperergic vasculitis, concluding that bleeding and clotting times were always normal.

The long-standing "wanderings" of Bulgarian authors still give them a reason to conclude that Schönlein-Henoch is an allergic disease. All this had led to the belief that the disease is

nothing more complicated than the described above and therefore followed several decades in which there are no scientific reports on the problem.

In 1993 Iv. Marinovsky (11) published a comprehensive article on the acute surgical problem in children with HSP. In 1996 a scientific paper by G. D. Georgiev was published (12), in which he shared the practical approaches in the treatment of HSP.

HSP is usually diagnosed based on the clinical features: purpuric rash, colic-like abdominal pain, arthralgia, and hematuria. The American College of Rheumatology describes the criteria for diagnosing HSP. (13) According to them and for this classification, a patient is considered to have HSP if at least two of the four criteria are present. The presence of two or more of them gives reliability in 87.1% and specificity in 87.7%. (13)

Table 1. Criteria for HSP

1. Palpable purpura	Slightly raised palpable hemorrhagic skin lesions, non-thrombocytopenic
2. Age over 3 years. at the initial manifestation of the disease	Age over 3 years at the initial manifestation of the disease
3. Bowel angina	Diffuse abdominal pain exacerbated by food, infection, or diagnosis of intestinal ischemia, usually involving bloody diarrhea
4. Presence of granulocyte deposition in the walls of arterioles and venules on biopsy	Histological changes showing granulocytes in the walls of arterioles and venules

HSP is a disease mediated by immune complexes. Vascular deposition of IgA-dominant immune complexes typically induces endothelial cell damage through the inflammatory action of cytokines and the involvement of inflammatory cells. (14, 15) Abnormally glycosylated IgA1 aggregates into macromolecular complexes that activate the alternative complement pathway and attract inflammatory cells. (16) Secretory mucosal IgA (SIgA) provides immune exclusion by binding to pathogens in a hydrophilic confirmation of a sheath that is repelled by mucosal surfaces. Besides, IgA can neutralize bacterial products, agglutinate microbes, and interfere with bacterial motility. (17) IgA1 has an elongated hinge region due to the insertion of two octapeptide repeats. They have 3 to 6 common O-glycan sites to which O-glycans can be attached during glycosylation. IgA can activate complement proteins, but cannot

activate the classical complement pathway because it lacks a C1q binding site.

Besides, IgA can bind and activate multiple receptors, and one of them is the transfer receptor CD71, which is universally expressed as a transmembrane glycoprotein. Overexpression of this receptor in mesenchymal cells is thought to facilitate the deposition of IgA-containing immune complexes in the mesangium. (18)

The prototype IgA1 receptor FcαRI is presented as a transmembrane receptor of soluble myeloid cells (sCD89). It may form immune complexes with IgA and is thought to play a role in the progression of IgA nephropathy. (19) Monomeric IgA can bind to FcαRI, but not crosswise, eliciting an anti-inflammatory response. Monovalent binding to IgA results in the formation of intracellular structures called inhibisomes. (20) This process is called inhibitory immunoreceptor

tyrosine signaling (ITAMI) and leads to a decrease in the regulation of immune activation. (21, 22)

In contrast, binding of IgA immune complexes to neutrophil FcαRI causes activation of ITAMI signaling. FcαRI cross-linking results in a variety of anti-inflammatory functions such as phagocytosis, ROS production, cytokine and chemokine release, antibody-dependent cellular cytotoxicity (ADCC), and extracellular trap release. (19, 23) The activation of FcαRI induces the release of the chemoattractant LTB-4, which leads to neutrophil migration. (24) As neutrophils and IgA are present in IgA vasculitis lesions, the interaction between IgA and FcαRI likely plays a role in the pathogenesis of IgA vasculitis.

IgAN is characterized by IgA1 autoantibodies, but the antigen to which IgA1 binds is unknown. In IgA vasculitis, anti-endothelial cell antibodies (AECAs) are thought to be associated with the disease. (25)

Microorganisms most likely have similar antigenic structures as human vessel walls. Infections with these microorganisms lead to the production of cross-reactive AECA. (26) Ig AECA from IgAV patients is most likely to induce endothelial cells to produce cytokines such as IL-8, thereby promoting the inflammatory environment and inducing neutrophil chemotaxis. (27, 28) IgAN is characterized by IgA1 autoantibodies, but the antigen to which IgA1 binds is unknown. In IgA vasculitis, anti-endothelial cell antibodies (AECAs) are thought to be associated with the disease. (25) Microorganisms most likely have similar antigenic structures as human vessel walls. Infections with these microorganisms lead to the production of cross-reactive AECA. (26) AECA from IgAV patients is most likely to induce endothelial cells to produce cytokines such as IL-8, thereby promoting the inflammatory environment and inducing neutrophil chemotaxis. (27, 28)

1. Genetic factors and their role in the pathogenesis of IgAV

The incidence of IgAV varies between ethnic groups, being highest among Southeast Asians and lowest among Americans. (31) Although rare, familial IgAV aggregation has been reported. (32) When comparing genetic variants between healthy and IgAV patients,

the greatest difference was found in HLA genes. Variants HLA-DRB * 01 and HLA-DRB1 * 11 are associated with IgAV, while HLA-DRB1 * 07 is negatively associated with IgAV. (33) HLA genes encode MHC molecules that are important for T-cell antigen presentation.

2. Disorders of the coagulation system

Factor XIII (fibrin-stabilizing factor) decreases significantly during the acute phase of HSP and is a prognostic indicator of the severity of clinical manifestations of HSP. (36, 37)

vWF-predictor of vascular damage

The von Willebrand factor level can be used as a specific marker of vascular damage and HSP activity. It is a plasma glycoprotein synthesized by megakaryocytes (38) and endothelial cells (39) isolated from large and small veins, capillaries and arteries, the aorta, which mediates platelet adhesion to the sub-endothelium and platelet aggregation by binding to the injured vessel wall.

Accumulated data on elevated von Willebrand factor concentrations are considered a reliable index of vascular damage. The possible correlation of vWFAg with the size of the affected blood vessel is also discussed. (40, 41) The von Willebrand factor does not play the role of an acute phase reagent, but as a marker of vascular damage. Elevated vWFAg values reflect the increased amount of circulating endothelial factor due to vascular damage. Values return to normal when patients are in remission and remain above normal levels with continued symptoms. The evaluation of vWFAg and RiCoF can be accepted as reliable tests for monitoring disease activity.

The level of the von Willebrand factor depends on the disease activity and there is no relationship between factor XIII and clinical symptoms. (42) In a large study, factor XIII was shown to decrease only in severe clinical cases. (43) However, neither study evaluated both markers of inflammation and activated coagulation in patients with HSP. Levels of fibrinogen, D-dimers, and FDPs are significantly higher during the acute phase of the disease compared to controls. D-dimers and FDPs are more strongly associated with the overall clinical score of HSP than inflammatory markers such as the number of WBC, ANC, CRP.

D-dimers and FDPs can allow the clinicians to evaluate not only the effectiveness of treatment but also relapses, especially in young children. They also play an important role as indicators of GI tract involvement during the acute phase of HSP.

3. Immune imbalance in HSP

Due to the still existing ambiguities in the pathogenesis of HSP, it is important to examine both the immune parameters and the underlying mechanisms in children with HSP. An imbalance in the Th1 / Th2 ratio, over activity of Th2 cells, which can cause an increase in the synthesis and release of immunoglobulins, has been established. The percentage of NK cells is also reduced, as well as their immune function, which is associated with immune damage to the digestive tract and kidneys.

An established low level of IL-2 may reduce the immune function of NK cells. This affects the ability to remove foreign antigens and an increased risk of damage to the digestive and urinary systems. The increased number of B-cells is evidence that gastrointestinal involvement is associated with CD4 + and CD8 + imbalance.

4. Perspectives in the therapeutic approach in HSP

It is now generally accepted that HSP is a self-limiting disease. New knowledge on the pathogenic nature of HSP provides new directions and changes the current concept that HSP treatment is only supportive and symptomatic focused on controlling the severity of the clinical course, and not on its treatment itself.

Although newer drugs also require more research and experimentation, their expected effectiveness, based on new knowledge about the pathogenic mechanisms of HSP, motivates their use in the therapeutic plan in children with HSP.

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