MULTIFACTORIAL ETIOPATHOGENY OF HENÖCH-SCHÖNLEIN PURPURA IN PEDIATRIC AGE

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ABSTRACT

Henöch-Schönlein purpura is a small-vessel vasculitis characterized by an abnormal response of the immune system: immunoglobulin A (IgA), C3 and immune complex deposition in arterioles, capillaries and venules. The syndrome is mostly seen in children, but it may affect people of any age. It is more common in boys than in girls. The etiology of Henöch-Schönlein purpura is unknown. Multiple infectious agents as well as drugs, foods, and insect bites may trigger Henöch-Schönlein purpura. Susceptibility to HSP may have a genetic origin. Several reports suggest that deficiency of complement 4 (C4) from deletion of C4 genes predisposes patients to IgA nephropathy and HSP nephritis.

Keywords: Henöch-Schönlein purpura, vasculitis, child

HSP is the most common primary systemic vasculitis encountered in childhood and is characterized by inflammation of the small vessels. The consequence of this swelling is the tissue injury which can vary from vascular stenosis, occlusion, aneurysm to rupture of the vessel wall.

HSP is a part of the big classes of systemic vasculitis and it is a non-granulomatous small vessel vasculitis. European League Against Rheumatism (EULAR) and the Paediatric Rheumatology European Society (PRES) established in 2005 a new classification of these diseases. (1)

EPIDEMIOLOGY

Epidemiological studies have shown that the annual incidence of HSP varies between 125-180 cases per 1 million children (2,3). Although this condition can occur from 6 months of age until adulthood, 50% of cases occur in children under 5 years and 75% by the age of 10.

The disease is more common in male patients (4). It has been noted an increased incidence in winter and spring, suggesting the existence of infectious triggers and/or genetic susceptibility (2).

At least 50% of cases with HSP was preceded by an upper respiratory tract infection with group A hemolytic streptococcus beeing the most frequently isolated germ (5).

It has been reported in children with HSP the intervention of infections with adenovirus, parvovirus and *Mycoplasma pneumonie*.

Helicobacter pylori has been implicated in the gastrointestinal and extradigestive manifestations of HSP and also in Henöch-Schönlein nephritis (6).

A number of researchers showned that there are other factors that may precipitate the disease; drugs like penicillins, ampicillin, erythromycin, acetaminophen and NSAIDs are involved (7,9).

Food allergens, certain vaccines, insect bites and exposure to cold were considered triggers for the condition (9).

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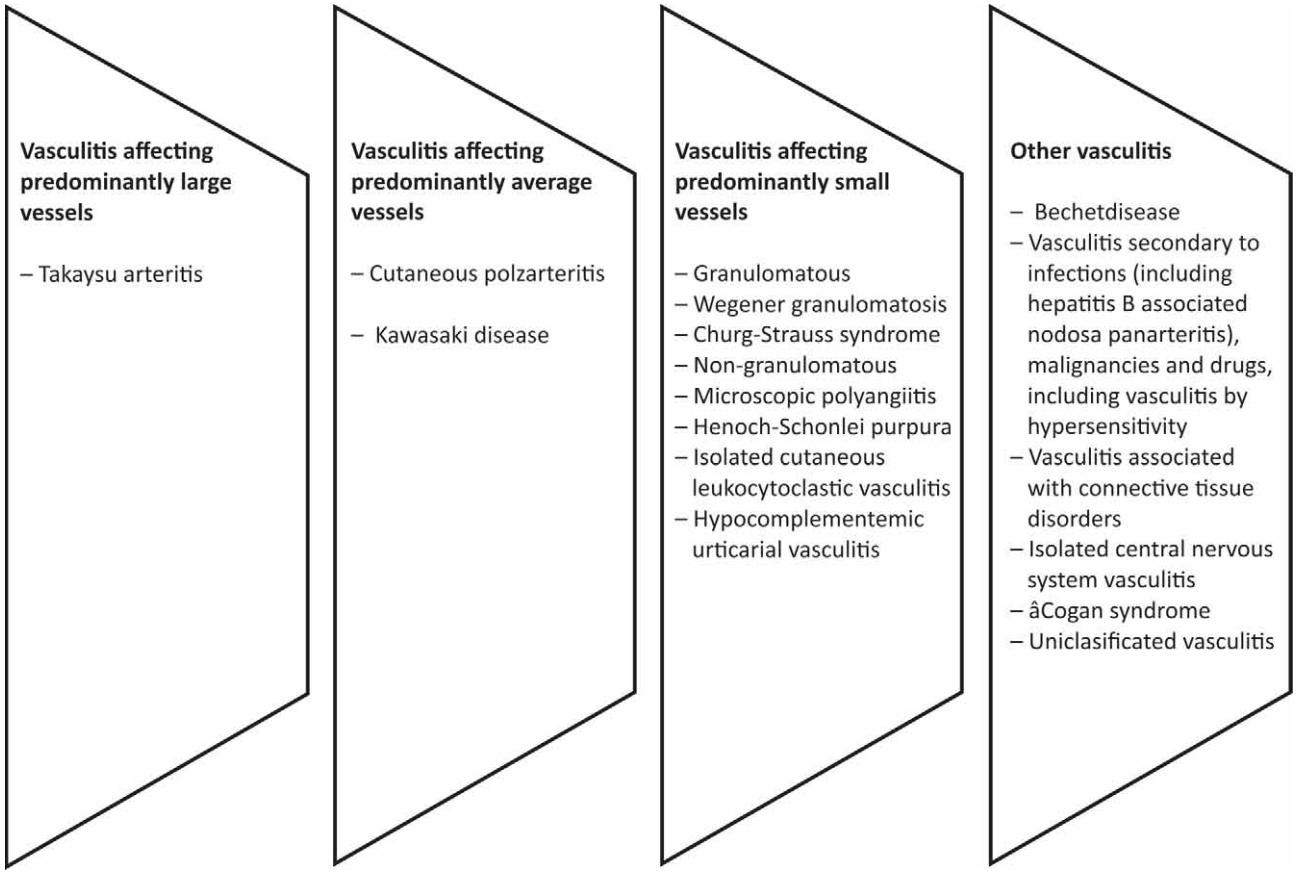

PATHOGENESIS

The pathogenic mechanisms of HSP are not very well understood. This IgA mediated vasculitis causes inflamation of small vessels. IgA immune dominant deposits are observed in the walls of small blood vessels and in the glomerular capillaries.

IgA abnormalities have been described, such as elevations of the levels of serum IgA, IgA-containing immune complexes, the IgA rheumatoid factor (RF), IgA, ANCA (anti-neutrophil cytoplasm) and AECA IgA (anti-endothelial cells) (10).

Biology of Ig A

In healthy patients, IgA is found in abundance in mucosal fluids but their serum concentration is low. In primates IgA are represented by two isotypes: IgA1 and IgA2. 6% of the secretion of IgA is represented by a Ig A2 subclass polymer, and has a secretory component synthetized by the glandular epithelial cells. About 90% of serum IgA is a IgA1 monomer.In Henöch-Schönlein nephritis mesangial deposits contain predominantly polymeric IgA1 and the secretory component is absent (10,11).

Origin of IgA; the role of synthesis and their inadequate clearance

Both IgA increased synthesis and decreased clearance have been involved in the pathogenesis of deposition of the IgA immune complex. The increase in production of the polymeric IgA of mucosal immune system as response to an antigen presented to the mucosa can be a potential mechanism of HSP production (11,12). *In vitro* B-cell hyperresponsiveness and T-specific response to antigenic stimulation has been reported in patients with IgA nephropathy and HSP (11,12,13). Clinical observations *in vivo* have demonstrated the involvement of infectious antigens as immunomodulators, with clinical association between mucosal infections and HSP (13).

Increased IgA secretion can be explained by a higher production, but also by a decreased clearance. Abnormal glycosylation of the Ig A1 binding-region may be responsible for the clearance alteration and storage of IgA, causing the clinical and histological changes in the HSP (12,13).

Some studies have demonstrated increased production of polymeric IgA in the mucosal cells of the tonsils and adenoids, while others report a de-

crease in the production of polymeric mucosal IgA and an increased production in the marrow bone (1, 14). Impaired IgA production favors the penetration of antigens and stimulate marrow exaggerated response (4).

It has been suggested that deposits of IgA represents practically rheumatoid factor (11). Serum levels of total IgA is increased in 40-50% of patients with HSP, with high values of both monomeric and polymeric IgA. There is an impairment in binding IgA1 with the liver sialoproteins (which normally facilitates clearance of circulating IgA) in patients with IgA nephropathy and HSP. (1,13,14).

Another unknown antigen can stimulate the production of IgA activating pathways that cause necrotizing vasculitis: immune complexes of IgA isotype or IgA autoantibodies (RF, ANCA, AECA) (10,14).

Abnormalities of complement and MAC system

Complement abnormalities have been described in HSP: lack of C2, C4 null phenotype and homozygous C4B deficiency. Other anomalies include glomerular deposition of C3 and properdin, decreased CH50 and C3d properdin elevated in the acute phase of the disease, suggesting activation of complement. However, studies of the activation of three multimolecular protein complexes of the complement were unable to demonstrate the role of its activation in the HSP (1,15).

IgA immune complexes lead to activation of complement, resulting the formation of the C5a chemotactic factors which in turn recruit polymorphonuclear neutrophils to the place of storage. Releasing the lysosomal enzymes because of the incorporation of immune complexes by polymorphonuclear leads to vessels destruction. Serum C5b-9 was shown to be significantly increased in many patients with HSP during relapse (1,16). Membrane attack complex (MAC) is also involved in endothelial damage. MAC has been found with IgA and C3 in the walls of skin vessels, the walls of the capillaries and in the mesangial glomerule (15).

Hisano et al. confirmed the presence of both complement activation pathways (alternate route and lectin route) in patients with HSP. These authors have shown that complement activation is initiated in situ in the glomerules. The lectin pathway of complement activation may play an important role in the development of advanced glomerular injury and persistent urinary abnormalities (17).

Proinflammatory factors in the pathogenesis of PHS

Traditional inflammatory mediators are involved in glomerular injury. Deposits of C3 and properdin without involvement of C1q and C4 are typical, suggesting the alternate pathway of complement activation. Despite the demonstrated presence of complement components in the cutaneous and renal biopsy, there is a controversy about its role in the pathogenesis of HSP. Some authors consider that co-Ig IgG accumulation can modulate the activity of the disease (1,17)

The role of cytokines, growth factors, chemokines and adhesion molecules in mesangial proliferation is subject of basic research. Interleukin 1 (IL-1), IL-6, platelet-derived growth factor (PDGF), tumor necrosis factor (TNF), oxygen free radicals, prostanoids, leukotrienes, vascular cell adhesion molecule-1 (VCAM-1) and circulating immunostimulatory protein (90 K) are involved (15,18). Proinflammatory cytokines are also playing a role in the pathogenesis of nephritis.

In the acute phase of the disease, serum TNF levels were significantly increased in patients with HSP and proteinuria comparing with patients without renal impairment. This observation suggests that elevated levels of TNF induce a series of functional and morphological changes in glomerular cells in the acute phase of the illness. Thus can be used as markers of HSP activity in patients with severe renal dysfunction (18).

Genetic susceptibility

Susceptibility to HSP has a genetic origin. Numerous reports suggest that C4 deficiency due to deletion of genes encoding C4 synthesis determines susceptibility to IgA nephropathy and Henöch-Schönlein nephritis. Japanese patients with HSP have an increased prevalence of C4 gene deletion, but this is not observed in the population of Italy, Spain, Kentucky or in the central and southern United States (19,20). HSP genetic susceptibility may be provided by the interaction of a number of loci, including major histocompatibility system (MHC).

Gene DQA1 * 301 seems involved, as suggested by a study and also DRB1 * 01 or DRB1 * 11, which facilitates the onset of disease. DRB1 * 07 gene appears to provide resistance to the disease. The allele gene of IL-1 receptor antagonist (IL1RN * 2) may be a marker gene in patients with HSP nephritis and also in those with IgA nephropathy with recurrent macroscopic hematuria (19,20,21).

Recent genetic studies in the region of Lugo, northwestern Spain, emphasized the role of non-MHC genes in susceptibility and increased risk of developing gastrointestinal events (22). Also the non MHC genes raise the probability to develop nephritis or nephrotic syndrome. (19,22).

CONCLUSIONS

Henöch-Schönlein purpura is one of the most common vasculitis in children. The etiology is not fully known; infectious factors, insect bites, food or drugs (antibiotics, antihistamines) and genetic causes are incriminated. Multifactorial etiopathogenesis suggests the complexity of investigations necessary to framing diagnostic and therapeutic approach.

REFERENCES

1. **Despina Eleftheriou; Michael J. Dillon; Paul A. Brogan; Advances in childhood vasculitis.** *Curr Opin Rheumatol***.** 2009; 21(4):411-418.
2. **Gonzalez-Gay. M.A., Garcia-Porrua. C.** Epidemiology of the vasculitides. *Rheum. Dis. Clin. North Am.* 2001, 27: 729-731.
3. **Trapani S., Micheli A., Grisolia F. et al.** Henoch Schonlein Purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin. Arthritis Rheum***.** 2005; 35: 143-152.
4. **Robson WLM, Leung AKC.** Henoch-Schonlein purpura. *Advances in Paediatrics* 1994; 41:163-94.
5. **Farley T.A., Gillespi S., Rasoulpour M.** Epidemiology of a cluster of Henoch-Schonlein purpura. *Am. J. Dis. Child***.** 1989, 143: 798-802.
6. **Novak J., Szekanecz Z., Sebesi J. et al.** Elevated levels of anti-Helicobacter pylori antibodies in Henoch-Schonlein purpura. *Autoimmunity.* 2003 36: 307-310.
7. **Garcia-Porrua, C., Gonzalez-Gay, M.A., Lopez-Lazaro, L.** Drug-associated cutaneous vasculitis in adulthood. Clinical and epidemiological associations in a defined population of Northwestern Spain. *J. Rheumatol***.** 1999; 26: 1942-1945.
8. **Gonzalez-Gay M.A., Calvino M.C., Vazquez-Lopez M.E. et al. 2004.** Implications of upper respiratory tract infections and drugs in the clinical spectrum of Henoch- Schonlein purpura in children. *Clin. Exp. Rheumatol***.** 2004; 22:781-785.
9. **Schaller J.G: Rheumatic diseases of childhood; in Bherman R.E., Kliegman R.M. (eds).** Nelson Textbook of Pediatrics 14th edition W.B. Saunders Co., Philadelphia 1992, 610-626.
10. **Lin J.J. Stewart C.L., Kaskel F.J., Fine R.N.** IgG and IgA classes of anti-neutrophil cytoplasmic antibodies in a 13 year old girl with recurrent Henoch-Schonlein purpura. *Pediatr Nephrol* 1993; 7:143-146.
11. **Ronda N., Esnault VLM, Layward L., et al.** Antineutrophil cytoplasm antibodies (ANCA) of IgA isotype in adult Henoch-Schonlein purpura. *Clin Exp Immunol* 1994; 95:49-55.
12. **Saulsbury F.T.** Henoch-Schonlein purpura in children. Report of 100 patients and review of the literature. *Medicine (Baltimore)* 1999; 78: 395-408.
13. **Saulsbury F.T.** Henoch-Schonlein purpura. *Curr. Opin. Rheumatol***.** 2001; 13: 35-39.
14. **Tizard E.J.** Henoch-Schonlein purpura. *Arch. Dis. Child***.** 1999; 80: 380-387.
15. **Miguel A. Gonzalez-Gay, Carlos Garcia Porrua and Jose A. Miranda-Filloy, Henoch Schonlein,** Purpura in Mason J.C. and Pusey C.D., *The kidney in Systemic Autoimmune System Disease***.** Oxford, Elsevier, 2008; 241-254.
16. **Kawana S., Nishiyama S.** Serum SC5b-9 (terminal complement complex) level, a sensitive indicator of disease activity in patients with Henoch-Schonlein purpura. *Dermatology* 1992; 184: 171-176.
17. **Hisano S., Matsushita M., Fujita T., et al.** Activation of the lectin complement pathway in Henoch-Schonlein purpura nephritis. *Am. J. Kidney Dis***.** 2005; 45: 295-299.
18. **Ha T.S.** The role of tumor necrosis factor-alpha in Henoch-Schonlein purpura. *Pediatr. Nephrol.* 2005; 20: 149-152.
19. **Amoli M.M., Calvino M.C., Garcia-Porrua C. et al.** Interleukin 1beta gene polymorphism association with severe renal manifestations and renal sequelae in Henoch-Schonlein purpura. *J. Rheumatol*. 2004; 31: 295-299.
20. **Amoli M.M., Thomson W., Hajeer A.H. et al.** HLA DRB1* 01 association with Henoch-Schonlein purpura in patients from northwest Spain. *J. Rheumatol*. 2001; 28: 1266-1270.
21. **Amoroso A., Berrino M., Canale L., et al. I**mmunogenetics of Henoch-Schonlein disease. *Eur. J. Immunogenet***.** 1997; 24: 323-327.
22. **Martin J., Paco, L. Ruiz, M.P. et al. I**nducible nitric oxide synthase polymorphism is associated with susceptibility to Henoch-Schonlein purpura in Northwestern Spain. *J. Rheumatol*. 2005; 32: 1081-1086.