



Epidemiology of Henoch-Schönlein purpura

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Epidemiology is the study of diseases and the factors associated with the occurrence of diseases in defined populations. The epidemiology of most diseases can be viewed on two levels. Traditional macro-epidemiology examines the influence of age, gender, ethnic background, geography, environmental factors, and other variables on the susceptibility to a given disease. Micro-epidemiology examines the genetic and molecular factors that render some individuals or populations susceptible to a disease and others protected. This paper will review the macro-epidemiology of Henoch-Schönlein purpura (HSP) and discuss recent advances in understanding the micro-epidemiology of HSP.

■ MACRO-EPIDEMIOLOGY

HSP is an acute vasculitis that primarily affects children. The dominant clinical manifestations include purpura, arthritis, abdominal pain, gastrointestinal bleeding, and nephritis. The clinical features of HSP are a consequence of widespread leukocytoclastic vasculitis owing to IgA deposition in vessel walls. IgA deposition in the renal mesangium causes nephritis in some patients.

HSP is the most common acute vasculitis affecting children, with an incidence of approximately 10 cases per 100,000 children per year.¹⁻⁴ Most studies on the incidence of HSP have been performed in Europe and the Middle East. There is little available information comparing the incidence of HSP in other parts of the world or in populations of widely disparate ethnic origins. HSP has been reported in patients as young as 6 months of age to as old as 86 years, but the vast majority of patients with HSP are young children. The mean age of the patients in most large series is 6 years.⁴⁻⁶ Approximately 75% of children are less than 8 years of age, and 90% are less than 10 years of age. Most studies report slightly more boys affected (60%) than girls (40%).

HSP occurs throughout the year, but a number of studies have noted seasonal skewing, with most patients presenting from fall through spring, and a paucity of cases during the summer months.⁴⁻⁶ Clusters or epidemics of HSP are rare. Farley et al⁷ reported a cluster of 16 cases of HSP, including 2 pairs of siblings during a 7-month period

in Connecticut. However, other large epidemiologic studies have found no evidence of geographic or temporal clustering of cases.^{1,4} Moreover, the occurrence of multiple cases within a family is very uncommon.

Schönlein was the first to observe that respiratory infections commonly precede the onset of symptoms, an observation that has subsequently been made by many authors. Given the epidemiology of HSP (a disease affecting young children with a peak occurrence during the fall and winter months), it is not surprising that a large proportion of children have a history of upper respiratory infection. Nevertheless, there have been very few controlled studies examining the incidence of infections with specific pathogens in children with HSP compared to control children.

Of all the pathogens linked to HSP, group A beta-hemolytic streptococcus (GABS) has been the most extensively studied. Gairdner⁸ first proposed that HSP was associated with GABS infection in 1948. In Gairdner's study, 50% of patients but only 10% of controls had a positive throat culture for GABS. Subsequent studies, many without controls, found positive throat cultures for GABS in 10-30% of patients^{1-3,5} and increased antistreptolysin O (ASO) titers in 20-50% of patients.^{1,2,5} Al-Sheyab et al⁹ reported a statistically significantly higher proportion of children with HSP had increased ASO titers compared to controls. Other studies, however, have found no increased incidence of concomitant or preceding GABS infection in children with HSP compared to control children.^{10,11} Taken together, these results indicate that a substantial minority of children with HSP have concurrent or recent GABS infection, but most cases have no direct link to GABS infection.

Anecdotal reports have implicated virtually every microbial pathogen in the etiology of HSP. However, very few studies have compared the incidence of infection with a specific pathogen in HSP versus controls. For example, there are a number of reports of parvovirus B19 infection in patients with HSP, but a recent study demonstrated the incidence of acute parvovirus B19 infection was no different in children with HSP compared to control children.¹² In addition to infections, HSP has been associated with a wide variety of drugs and other agents.⁴⁻⁶ Nevertheless, none of these agents have been proved to be associated with HSP in controlled studies. Thus, despite extensive efforts and scores of anecdotal reports, there appears to be no single pathogen or environmental agent that has emerged as a dominant precipitating cause of HSP.

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There are important differences in the epidemiology and the clinical features of HSP in adults compared to children. The incidence of HSP in adults is about one-tenth that of children, with available data indicating 13-14 cases per 1,000,000 adults per year.^{13,14} In several large series, the mean age of adults with HSP was approximately 50 years. Men and women are affected with equal frequency. There is little seasonal variability, and preceding infections are less common in adults compared to children. HSP is often more severe in adults. Nephritis occurs in 50-80% of adults, but only 20-40% of children. Ten to twenty percent of adults with HSP nephritis develop end-stage renal disease compared to 1% of children.^{15,16}

■ MICRO-EPIDEMIOLOGY

Although the etiology is unknown, it is clear that IgA plays a pivotal role in the pathogenesis of HSP. HSP is associated with a variety of abnormalities involving IgA, including increased serum IgA concentrations, IgA-containing circulating immune complexes, and IgA deposition in vessel walls and renal mesangium. There are two subclasses of IgA—IgA1 and IgA2. IgA1 accounts for 80-90% of serum IgA, while secretory IgA is composed of roughly equal proportions of IgA1 and IgA2. It is noteworthy that HSP is associated with abnormalities involving only IgA1, but not IgA2. The reasons for the exclusive involvement of IgA1 in the immunopathogenesis of HSP are beginning to emerge.

One important difference between IgA1 and IgA2 involves the hinge region of the heavy chain, and the glycosylation sites therein. IgA1 contains a proline-rich hinge region between the CH1 and CH2 domains of the heavy chain. It is composed of 18 amino acids, of which 5 are O-linked glycosylation sites. The basic structure is N-acetylgalactosamine (GalNAc) O-linked to serine or threonine. The oligosaccharide chain is usually extended by the addition of galactose (Gal) in β1,3 linkage with GalNAc, and with one or two sialic acid residues in α2,3 linkage with Gal or α2,6 linkage with GalNAc. IgA2 molecules do not contain a heavy-chain hinge region and, thus, no O-linked oligosaccharides.

■ REFERENCES

1. Nielsen HE. Epidemiology of Schönlein-Henoch purpura. *Acta Paediatr Scand* 1988; 77:125-131.
2. Abdel-Al YK, Hejazi Z, Majeed HA. Henoch-Schönlein purpura in Arab children. Analysis of 52 cases. *Trop Geogr Med* 1990; 42:52-57.
3. Al-Sheyyab M, El-Shanti H, Ajlouni S, Batiha A, Daoud AS. Henoch-Schönlein purpura: clinical experience and contemplations on a streptococcal association. *J Trop Pediatr* 1996; 42:200-203.
4. Calvino MC, Llorca J, Garcia-Porrúa C, Fernandez-Inglesias JL, Rodriguez-Ledo P, Gonzalez-Gay MA. Henoch-Schönlein purpura in children from northwestern Spain. A 20-year epidemiologic and clinical study. *Medicine* 2001; 80:279-290.
5. Robson WLM, Leung AKC. Henoch-Schönlein purpura. *Adv Pediatr* 1994; 41:163-194.
6. Saulsbury FT. Henoch Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine* 1999; 78:393-409.
7. Farley TA, Gillespie S, Rasoulpour M, Tolentino N, Hadler JL, Hurwitz E. Epidemiology of a cluster of Henoch-Schönlein purpura. *Am J Dis Child* 1989; 143:798-803.
8. Gairdner D. The Schönlein-Henoch syndrome (anaphylactoid purpura). *Q J Med* 1948; 17:95-122.

In order to understand the exclusive involvement to IgA1 in the pathogenesis of HSP, attention has focused on the hinge region glycosylation of IgA1 in HSP and also in IgA nephropathy (IgAN). The latter disorder shares a number of clinical and immunologic features in common with HSP. Importantly, the immunopathogenesis of IgAN also involves IgA1 exclusively. Although most of the work in this area has involved patients with IgAN, there is clear relevance to the pathogenesis of HSP.

Using a variety of techniques, a number of investigators have found that the hinge region O-linked glycans of IgA1 in patients with IgAN are deficient in galactose,¹⁷ sialic acid,¹⁸ or both.¹⁹ Despite extensive work in patients with IgAN, there have been only two studies examining IgA1 glycosylation in patients with HSP. Saulsbury²⁰ reported that the hinge region of IgA1 in children with HSP was deficient in sialic acid, but the content of Gal and GalNAc were normal. Allen et al²¹ reported diminished hinge region Gal content in IgA1 from HSP patients with nephritis, but no difference in IgA1 glycosylation in HSP patients with no nephritis compared to controls.

The mechanisms of aberrant glycosylation of IgA1 in HSP and IgAN remain unclear. Nevertheless, aberrant glycosylation may have important consequences for the IgA1 molecule, and may explain many of the immunologic and histologic features of HSP. IgA1 molecules that are deficient in sialic acid or Gal have a tendency to aggregate and form macromolecular complexes.^{18,22} In addition, sialic acid and Gal deficient hinge regions interact with IgG antiglycan antibodies to form IgA-IgG complexes.²² Lastly, aberrantly glycosylated IgA1 has a propensity to deposit in the kidney.^{23,24}

In summary, the macro-epidemiology of HSP has been well documented over the past 200 years. Nevertheless, macro-epidemiology has not provided definitive information concerning the etiology of HSP. The micro-epidemiology of HSP is far less clear, but understanding of this aspect of the epidemiology will ultimately shed light on the etiology of HSP.

9. Al-Sheyyab M, Batiha A, El-Shanti H, Daoud A. Henoch-Schönlein purpura and streptococcal infection: a prospective case-control study. *Ann Trop Paediatr* 1999; 19:253-255.
10. Ayoub EM, Hoyer J. Anaphylactoid purpura: streptococcal antibody titers and β1c-globulin levels. *J Pediatr* 1969; 75:193-201.
11. Bywaters EGL, Isdale I, Kempton JJ. Schönlein-Henoch purpura. Evidence for a group A β-haemolytic streptococcal aetiology. *Q J Med* 1957; 26:161-175.
12. Ferguson PJ, Saulsbury FT, Dowell SF, Torok TJ, Erdman DD, Anderson LJ. Prevalence of human parvovirus B19 infection in children with Henoch-Schönlein purpura. *Arthritis Rheum* 1996; 39:880-881.
13. Watts RA, Jolliffe VA, Grattan CEH, Elliot J, Lockwood M, Scott DGI. Cutaneous vasculitis in a defined population—clinical and epidemiological associations. *J Rheumatol* 1998; 25:920-924.
14. Gonzalez-Gay MA, Garcia-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997. *Medicine* 1999; 78:292-308.
15. Tancrede-Bohin E, Ochonisky S, Vignon-Pennamen MD, Flageul B, Morel P, Rybojad M. Schönlein-Henoch purpura in adult patients. *Arch Dermatol* 1997; 133:438-442.
16. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, Garcia-Fuentes M, Gonzalez-Gay MA. Henoch-Schönlein purpura in

- adulthood and childhood. Two different expressions of the same syndrome. *Arthritis Rheum* 1997; 40:859-864.
17. Allen AC, Bailey EM, Barratt J, Buck KS, Feehally J. Analysis of IgA1 O-glycans in IgA nephropathy by fluorophore-assisted carbohydrate electrophoresis. *J Am Soc Nephrol* 1999; 10:1763-1771.
 18. Hiki Y, Iwase H, Kokubo T, Horii A, Tanaka A, Nishikido J, Hotta K, Kobayashi Y. Association of asialo-galactosyl β 1-3 N-acetylgalactosamine on the hinge with a conformational instability of jacalin-reactive immunoglobulin A1 in immunoglobulin A nephropathy. *J Am Soc Nephrol* 1996; 7:955-960.
 19. Odani H, Hiki Y, Takahashi M, Nishimoto A, Yasuda Y, Iwase H, Shinzato T, Maeda K. Direct evidence for decreased sialylation and galactosylation of human serum IgA1 Fc O-glycosylated hinge peptides in IgA nephropathy by mass spectrometry. *Biochem Biophys Res Comm* 2000; 271:268-274.
 20. Saulsbury FT. Alterations in the O-linked glycosylation of IgA1 in children with Henoch-Schönlein purpura. *J Rheumatol* 1997; 24:2246-2249.
 21. Allen AC, Willis FR, Beattie TJ, Feehally J. Abnormal IgA glycosylation in Henoch-Schönlein purpura restricted to patients with clinical nephritis. *Nephrol Dial Transplant* 1998; 13:930-934.
 22. Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. *J Clin Invest* 1999; 104:73-81.
 23. Hiki Y, Kokubo T, Iwase H, Masaki Y, Sano T, Tanaka A, Toma K, Hotta K, Kobayashi Y. Underglycosylation of IgA1 hinge plays a certain role for its glomerular deposition in IgA nephropathy. *J Am Soc Nephrol* 1999; 10:760-769.
 24. Allen AC, Bailey EM, Brenchley PEC, Buck KS, Barratt J, Feehally J. Mesangial IgA1 in IgA nephropathy exhibits aberrant O-glycosylation: observations in three patients. *Kidney Int* 2001; 60:9699-73.