

## Henoch-Schönlein Purpura

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Henoch-Schönlein purpura (HSP) is a small vessel vasculitis that annually affects 10 to 20 children per 100,000 population. It is the most common vasculitis of childhood. Although HSP is seen in infancy through adulthood, most documented cases affect children; more than 75% of those diagnosed as having HSP are younger than 10 years, with a peak incidence at 4 to 6 years. White and Asian children are most commonly affected, whereas African American children are least commonly affected. Male predominance among children approaches 2:1. The most recent consensus criteria published in 2010 by the European League Against Rheumatism and the Paediatric Rheumatology European Society state that for diagnosis of HSP, palpable purpura should be accompanied by at least one of the following: abdominal pain, predominance of IgA deposition on a biopsy specimen, arthritis or arthralgia, or renal involvement indicated by hematuria/proteinuria. HSP often follows an upper respiratory tract infection, with most cases occurring in the fall and winter. Although many cases do not have a specifically identified infectious trigger, a variety of viral and bacterial agents have been associated with HSP, group A  $\beta$ -hemolytic streptococcus being the most common. Pathogenesis has been linked to IgA<sub>1</sub>, a subclass of IgA, and its deposition is noted in the glomerulus, the skin, and the blood vessels of the gastrointestinal (GI) tract. Abnormally O-glycosylated IgA<sub>1</sub> has been identified in patients with HSP nephritis and in patients with IgA nephropathy, a disease indistinguishable from HSP on renal biopsy.

The hallmark of HSP is cutaneous palpable purpura, often involving the lower extremities and buttocks. The appearance of the rash in this pattern reflects its tendency to distribute in pressure-dependent areas, so that in infants the rash may actually appear in upper body areas, such as the upper extremities or face. Lesions, which arise in crops and last 3 to 10 days, vary in size from petechiae to large, confluent, palpable ecchymoses. Although HSP is largely a clinical diagnosis, a skin biopsy specimen would reveal leukocytoclastic vasculitis or granulocytic infiltration of the small vessels, along with IgA deposition in the vessel walls. A nonpitting edema that involves the scalp, face, trunk, and/or extremities is also common, especially in infants and young children. This swelling does not correlate with the degree of proteinuria or level of serum albumin, although patients with HSP may also have pitting edema as a consequence of protein loss in the urine.

GI involvement is observed in as many as 75% of patients, who often present with diffuse, colicky pain. Commonly, the IgA vasculitis of HSP affects the vessels of the bowel wall, resulting in bleeding from the upper and lower GI tracts and intestinal edema. The bowel edema may also lead to the complication of intussusception; the reported incidence varies from 0.6% to 3.5%. Other major complications, although rare, include bowel ischemia, necrosis, and perforation. Even without frank hemorrhage, the incidence of GI bleeding is high: guaiac-positive

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stools may be seen in more than 50% of patients. As with skin lesions, a biopsy specimen of the intestine would reveal a leukocytoclastic vasculitis with vascular IgA deposits.

Joint involvement is common in HSP, affecting up to 80% of patients. Arthritis or arthralgia is often migratory and principally involves the large joints of the lower extremities. Joints can be painful and swollen. Although ambulation may be limited from arthralgia during the illness, the joint involvement does not lead to permanent articular damage.

Kidney disease, which affects 30% to 50% of patients with HSP, poses the main risk for morbidity, highlighting the importance of early and frequent follow-up of patients. Subclinical renal involvement can be detected with screening urinalyses and blood pressure checks. Severity ranges from isolated microscopic hematuria, with or without mild proteinuria, to crescentic glomerulonephritis that quickly progresses to end-stage kidney disease. Most patients who develop kidney disease have signs of renal involvement within 1 month of diagnosis and 97% within 6 months. Hematuria is a common finding on dipstick testing and often resolves with no long-term sequelae. However, hematuria and heavy proteinuria (specifically, nephrotic range proteinuria) portend a worse long-term outcome. Affected patients have a higher likelihood of developing chronic kidney disease and/or hypertension: 20% vs less than 2% in patients who have only isolated microscopic hematuria or mild proteinuria. However, rarely, these patients are also at risk for progression to end-stage kidney disease. A renal biopsy is indicated with suspicion of a nephritic or nephrotic syndrome, with or without evidence of acute kidney injury on serum studies: HSP is indicated by IgA immune complex deposition in the renal mesangium, accompanied by injury that ranges from mild mesangial proliferation to severe glomerulonephritis with crescent formation.

Other less common findings include disturbances of the central nervous system, although, rarely, the vasculitis of HSP can result in encephalopathy or seizures. In boys, scrotal involvement can occur, with findings of swelling, pain, and tenderness that mimic testicular torsion. Pulmonary involvement has also been reported, usually in adults and manifesting as alveolar hemorrhage or interstitial disease.

Although HSP classically presents as a purpuric rash followed by abdominal symptoms and arthralgias, it can vary widely in timing and severity of symptoms. For example, abdominal pain manifests before the rash in up to 30% to 40% of cases, and joint symptoms can be the presenting

symptom in 15% to 25% of patients. Abdominal pain associated with HSP can also present as an acute abdomen, and joint involvement may mimic rheumatic illnesses, such as rheumatoid arthritis or systemic lupus erythematosus. Taken together, these variations in presentation highlight the importance of keeping HSP in the differential diagnosis, even in the absence of rash, and providing early follow-up.

No laboratory tests are specific to HSP, making it largely a clinical diagnosis. The complete blood cell count is generally normal, without thrombocytopenia but sometimes revealing a leukocytosis. Standard coagulation study results are normal. The serum IgA level is elevated in approximately half of affected children, but the IgA level does not correlate with disease severity. The erythrocyte sedimentation rate is sometimes but not always elevated. Laboratory evaluation may prove more useful in eliminating other potential causes for similar symptoms. Normal serum antinuclear antibody, double-stranded DNA, antineutrophil cytoplasmic antibody, and complement C<sub>3</sub> and C<sub>4</sub> levels can help to distinguish HSP from other vasculitic processes, such as systemic lupus erythematosus or antineutrophil cytoplasmic antibody vasculitis. Absence of hypocomplementemia with a negative streptococcal test or ASO titer result may be useful in distinguishing HSP from a poststreptococcal glomerulonephritis, although streptococcal infection is associated with HSP in approximately one-third of cases. Perhaps the most important laboratory test to obtain with HSP is the urinalysis. Because renal disease is the leading cause of morbidity in HSP, following up serial urinalyses for urine protein-creatinine ratios (if urine protein is detected) is warranted for at least 6 months after diagnosis, with at least biweekly monitoring during the first 2 months after initial presentation.

Most often HSP is a self-limiting illness, with resolution of symptoms within 4 to 6 weeks of onset. One-third of patients experience a recurrence or relapse, usually within 1 year of initial presentation. However, long-term follow-up is important because complications such as hypertension and chronic kidney disease have been observed up to 10 years after an HSP episode. Treatment of HSP is largely supportive. Nonsteroidal anti-inflammatory drugs are helpful for joint pain, although caution must be exercised with their use if there is evidence of renal involvement. Corticosteroids are often used to ameliorate abdominal complications, and renal involvement may warrant treatment with additional immunosuppressive therapies, either alone or in combination: the alkylating agent cyclophosphamide; calcineurin

inhibitors, such as cyclosporine or tacrolimus; or cell cycle inhibitors, such as mycophenolate mofetil. Other treatment options include intravenous immunoglobulin, plasmapheresis, and ultimately transplantation if HSP progresses to end-stage renal disease.

Most cases of HSP are mild (mild abdominal and little or no renal involvement) and have an excellent prognosis; long-term sequelae most often affect patients with renal involvement. Even in this subset of patients, those with no more than microscopic hematuria or mild proteinuria will likely have full resolution of renal symptoms and good long-term outcome.

**COMMENT:** Despite how much we have studied group A streptococcus (GAS), how much we still do not understand about this all too common pathogen is humbling. Apparently, custom cannot stale its infinite variety. It triggers a multitude of immune reactions that can precipitate diseases as diverse as acute rheumatic fever, poststreptococcal glomerulonephritis, and, of course, HSP. Although not yet proven, GAS infection has also been proposed as the inciting cause of

pediatric autoimmune neuropsychiatric disorders associated with streptococci (so-called PANDAS). We can prevent acute rheumatic fever with timely penicillin, although we still do not know exactly what the link is between GAS and rheumatic disease. Why does treatment prevent acute rheumatic fever after pharyngitis but not poststreptococcal glomerulonephritis? Can GAS infection really set off an autoimmune cascade that results in obsessive-compulsion and tics?

Moving from immunopathology to the bedside, the rash of HSP may be its *sine qua non*, but, as Dr Reid-Adam points out, with this disease it is not unusual for the cart to come before the horse. I learned this personally when long ago as an intern on call I was asked by a nurse to look at the erupting rash on a 16-year-old boy. He had been admitted several days before with more than 3 weeks of abdominal pain, excruciating enough that he had become dependent on opiates. He had large, palpable purpuric lesions around both ankles: eureka, HSP!

– Henry M. Adam, MD  
*Editor, In Brief*

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