Clinical update: Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is an acute small-vessel leucocytoclastic vasculitis. HSP is the most common vasculitis in children, with an incidence of about 10 cases per 100 000 a year.1,2 In most series, boys are affected more often than girls. Although it can occur at any age, HSP is overwhelmingly a disease of childhood. The mean age of patients is 6 years; 75% of patients are under 8 years of age and 90% are less than 10 years of age.1,3 The clinical features of HSP may be atypical at the extremes of age. The severity tends to be milder in infants under 2 years of age and worse in adults. Most patients present from autumn to spring, and HSP often follows a respiratory infection. A wide variety of pathogens, drugs, and other environmental exposures have been associated with HSP. Of all pathogens linked to HSP, group A β-haemolytic streptococcus has been the most studied. Positive throat cultures have been reported in 10–30% of patients, and titres to anti-streptolysin O are raised in 20–50% of patients.1–3 Thus a substantial minority of patients have concomitant or recent streptococcal infection, but most cases have no direct link to streptococcal infection.

Although the cause is unknown, it is clear that IgA has a pivotal role in the pathogenesis of HSP. There are two subclasses of IgA, IgA1 and IgA2, but only IgA1 is involved in HSP. The clinical manifestations of HSP are a consequence of widespread vasculitis resulting from IgA1 deposition in vessel walls and the renal mesangium.4 The reasons for the exclusive involvement of IgA1 in HSP remain unclear. However, IgA1, unlike IgA2, contains a hinge region with multiple O-linked glycosylation sites.4 Two studies showed diminished glycosylation of the hinge region of IgA1 in patients with HSP.5,6 IgA1 molecules with diminished hinge-region glycosylation are prone to aggregate into macromolecular complexes. These complexes activate the alternative pathway of complement, and then deposit in the renal mesangium.4

The clinical features of HSP have been amply documented in reports spanning 200 years.1,3 The major clinical features of HSP are shown in the table and other infrequent complications are shown in the panel.

Cutaneous purpura is the essential element in the diagnosis of HSP. The characteristic rash consists of palpable purpuric lesions 2–10 mm in diameter. Pinpoint petechiae and coalescent ecchymoses may be scattered among these lesions. The purpura is concentrated on the buttocks and lower extremities, but it is not restricted to those areas.

Arthritis is the second most common feature of HSP, occurring in roughly 75% of patients and most often affecting the knees and ankles. The joints of the upper extremities are involved in a few patients. HSP arthritis is typically painful and often inhibits walking. It is important to remember that arthritis may precede the onset of the purpura by up to a week in 15–25% of patients.1,3

Gastrointestinal involvement occurs in 50–75% of patients. Colicky abdominal pain, vomiting, and gastrointestinal bleeding are the dominant features. Gastrointestinal bleeding is usually occult, but 30% of patients have grossly bloody or melanotic stools. Intussusception has been reported in 1–5% of patients. The intussusceptions associated with HSP are ileoileal in most patients. Thus abdominal ultrasonography or computed tomography are the preferred diagnostic modalities if intussusception is suspected in a patient with HSP. Gastrointestinal signs and symptoms may precede the onset of purpura by up to 2 weeks in 10–20% of patients.1,3 Gastrointestinal symptoms before the onset of the rash may simulate several inflammatory or surgical diseases of the bowel. The correct diagnosis becomes evident with the appearance of the typical rash.

Renal involvement occurs in 40–50% of patients. Microscopic haematuria is the most common finding.

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<th>Proportion of patients</th>
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<tr>
<td>Purpura</td>
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<td>Arthritis</td>
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<td>Abdominal pain</td>
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<td>Gastrointestinal bleeding</td>
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<td>Occult bleeding</td>
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<td>Gross bleeding</td>
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<td>Nephritis</td>
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<td>Microscopic haematuria</td>
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<td>Gross haematuria</td>
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<td>Proteinuria</td>
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<td>Nephrotic syndrome</td>
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<td>End-stage renal disease</td>
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<td>Recurrence of symptoms</td>
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Table: Major clinical manifestations in Henoch-Schönlein purpura
and 25% of patients also have gross haematuria. Proteinuria accompanies the haematuria in 60% of patients, but proteinuria alone is rarely a feature of HSP nephritis. Unlike arthritis and gastrointestinal involvement, nephritis rarely if ever precedes the onset of purpura. In fact, the onset of nephritis may be delayed for weeks or months after the appearance of other symptoms. About 75–90% of patients with nephritis develop urinary abnormalities within 4 weeks, and virtually all patients manifest urinary abnormalities within 3 months after the onset of other symptoms. Urinalysis should be done each week while the disease is active, then each month for 3 months thereafter. If all analyses are normal, nephritis is unlikely to occur. If at any time there is evidence of nephritis, long-term monitoring of urinalysis, protein excretion, renal function, and blood pressure is warranted until the urinary abnormalities resolve. Orchitis occurs in 10–20% of boys with HSP, and may mimic testicular torsion.

There are no distinctive or diagnostic laboratory abnormalities associated with HSP. The serum IgA concentration is increased in 50% of patients. Serum C3 or C4 concentrations are low in a few patients. Other laboratory studies are useful only to exclude other conditions that may resemble HSP. In most cases, HSP is a self-limited condition that lasts 4 weeks on average. A third of patients have recurrent symptoms, but the recurrences generally subside after 4–6 months. Nephritis is the one feature of HSP that may have chronic consequences, and the long-term prognosis heavily depends on the severity of nephritis. 30–50% of patients with nephritis have persistent urinary abnormalities for months or years, but fortunately only 1–3% of patients progress to end-stage renal disease. In general, patients with microscopic haematuria and trivial proteinuria have an excellent prognosis. However, late deterioration of renal function, years after nephritis, has been observed. By contrast, nephritis complicated by nephrotic syndrome has a poor prognosis.

Although the epidemiology, clinical features, and prognosis of HSP have been well documented, information about the most effective treatment has only recently emerged. A previous retrospective study suggested that corticosteroid therapy was effective in treating the abdominal pain. Recently, a randomised double-blind placebo-controlled study confirmed that prednisone in a dose of 1 mg/kg a day for 2 weeks, then tapered over 2 weeks, decreased the intensity and duration of gastrointestinal symptoms and the severity of joint symptoms. That study also showed that prednisone hastened the resolution of mild HSP nephritis. The use of corticosteroids early in the course of HSP does not seem to be effective in preventing the development of nephritis, however. Thus corticosteroid therapy is beneficial in ameliorating the gastrointestinal and joint symptoms and perhaps in shortening the duration of mild nephritis, but not in preventing delayed nephritis. Moreover, there is no evidence that corticosteroid therapy is effective in treating the purpura, shortening the duration of the disease, or preventing recurrences.

The treatment of severe HSP nephritis (nephrotic syndrome, diminished renal function and >50% crescents on renal biopsy) has not been rigorously studied. Niaudet and Habib reported that intravenous pulse methylprednisolone (30 mg/kg a day for 3 consecutive days) followed by oral corticosteroids was effective in
reversing severe nephritis and preventing progression. Others have reported the benefits of corticosteroids combined with cyclophosphamide, azathioprine, or cyclosporin in severe HSP nephritis.\textsuperscript{16-18} Thus early aggressive therapy is warranted in patients with severe nephritis.

Despite advances in our understanding of HSP, several questions remain. What is the difference between the children who develop HSP after various otherwise innocuous infections and the children who recover uneventfully from those infections? Why do only some patients develop nephritis? In other words, is there a genetic susceptibility to HSP or the complications of HSP? Are the previously reported abnormalities of IgA1 glycosylation clues to the genetic basis of HSP or mere epiphenomena? Is there a causal link between HSP and IgA nephropathy? IgA nephropathy shares several clinical and histological features with HSP.\textsuperscript{19} Moreover, IgA nephropathy, like HSP, is a condition that involves IgA1 exclusively, and IgA nephropathy is also characterised by aberrant glycosylation of IgA1.\textsuperscript{20} Searching for the answers to these questions should prove fruitful for clinical investigators, and finding the answers will ultimately reveal the cause of HSP.

Frank T Saulsbury
Division of Immunology and Rheumatology, Department of Pediatrics, University of Virginia Health System, Charlottesville, VA 22908, USA
fts@virginia.edu
I declare that I have no conflict of interest.