RHEUMATOLOGY

Henoch-Schönlein purpura

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Henoch-Schönlein purpura (HSP) is the most common vasculitic disease of childhood. It is a multisystem disease most commonly affecting skin, joints, gastrointestinal tract, and kidneys, but other organs may be affected. Epidemiological studies have shown HSP to have an annual incidence of approximately 13.5–18/100 000 children.[1 2] Although this is a condition that can occur from age 6 months to adulthood, 50% of cases occur in children under 5 years of age and 75% are under 10 years. In most reports HSP is more common in boys.[3]

The cause remains unknown although there is often an antecedent respiratory infection. Streptococcal infections have been implicated but other organisms including adenovirus, parvovirus, and mycoplasma have also been reported to precede HSP. The increased incidence in winter and spring supports an infectious trigger in a susceptible individual.

The American College of Rheumatology 1990 criteria for the classification of HSP aimed to identify diagnostic criteria to differentiate HSP from other vasculitic diseases.[4] The four criteria identified, of which two are necessary to make the diagnosis, are:

- age < 20 years at onset
- palpable purpura
- "bowel angina" (diffuse abdominal pain or bowel ischaemia usually with bloody diarrhoea)
- biopsy evidence of granulocytes in the walls of arterioles or venules.

The diagnosis is usually made after the appearance of the classic rash that primarily affects the extensor surfaces and may be urticarial or purpuric. Joint involvement occurs in 60–84% of cases and generally affects the ankles and knees. It is often the most incapacitating part of the initial illness. Gastrointestinal disease occurs in up to 76% of patients varying from colicky abdominal pain, nausea, and vomiting to intestinal haemorrhage, intussusception, pancreatitis, and hydrops of the gall bladder. There is an increased risk of renal disease in those with bloody stools.

The reported incidence of renal disease ranges from 20–100%.[5] In 80% of those with renal involvement it becomes apparent within the first four weeks of the illness. The remainder predominantly occurs over the next two months although a few are further delayed.[6] Haematuria with or without proteinuria is the most common renal feature. Acute nephritic syndrome may be associated with renal insufficiency, nephrotic syndrome, or both. Hypertension may be associated with acute nephritis but has also been reported in the absence of urinary abnormality.

Florid cerebral manifestations including seizures, paresis or coma are uncommon but have been reported.[7] It has been suggested that mild cerebral involvement presenting as headaches may occur in as many as a third of cases, and this may coincide with electroencephalogram abnormalities.[8] Scrotal involvement is not uncommon and occasionally resembles testicular torsion, which must be excluded. Other rare manifestations are cholecystitis and myocardial infarction. Interstitial lung disease with impairment of lung diffusion capacity has been reported, although this was clinically insignificant.[9]

Immunopathology

The pathogenetic mechanisms underlying HSP are poorly understood. Widespread abnormalities in IgA have been described including raised serum IgA concentrations, IgA immune complexes, IgA class antibodies such as IgA rheumatoid factor (RF),[10] IgA ANCA (antineutrophil cytoplasmic antibody),[11 12] and IgA AECA (antiendothelial cell antibody).[13] IgA deposits are also found in skin biopsies and deposited within glomeruli. There are reports of HSP developing in patients with IgA nephropathy[14] as well as simultaneous development of IgA nephropathy and HSP within sibships.[15] The strikingly similar histological abnormalities of mesangial IgA deposition suggest a common immunopathogenic process. IgA and IgG ANCA mirrored disease activity in a girl with frequently relapsing disease.[12] AECA has been detected in patients with vasculitic disorders such as Kawasaki disease and reported to be associated with renal involvement in HSP, although complement dependent cytotoxicity to glomerular endothelial cells has not been shown.[13]

Complement abnormalities have been described in association with HSP: C2 deficiency, homozygous null C4 phenotypes, and C4B deficiency. Other abnormalities including glomerular C3 and properdin deposition, low CH50 and properdin, and raised C3d concentrations in the acute phase of the disease have suggested complement activation. However, a study of three multimolecular complement

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activation protein complexes has failed to support a role for complement activation in HSP.[16]

Laboratory markers

There are no specific diagnostic markers of HSP. If present, anaemia is usually a result of gastrointestinal bleeding or associated with acute nephritis. Thrombocytosis is a feature that may be related to disease severity. Renal involvement results in haematuria with or without proteinuria, which may be in the nephrotic range. A rapidly progressive nephritis may result in renal insufficiency and requires histological assessment.

Von Willebrand factor antigen is synthesised by and is present in endothelial cells. High concentrations have been detected in patients with HSP as with other vasculitic diseases probably because of vascular endothelial damage.[17 18] A relation with disease activity has also been noted and this may be a useful marker of disease severity. Soluble thrombomodulin is derived from damaged endothelium and may reflect endothelial injury, and raised serum thrombomodulin concentrations have been demonstrated in patients with HSP nephritis.[13] Routine coagulation tests are normal while factor XIII activity has been reported to be low, especially in patients with severe gastrointestinal disease.[18]

Histology

Skin biopsy specimens show a leukocytoclastic vasculitis with perivascular infiltration of polymorphs and mononuclear cells. Necrosis of small blood vessels and platelet thrombi may also be seen. Immunostaining reveals IgA in most purpuric skin lesions and often also in non-affected areas. Renal biopsy findings may be graded according to the classification of the International Study of Kidney Disease in Children (ISKDC) from grades I–VI.[19] The primary lesion is an endocapillary proliferative glomerulonephritis involving both endothelial and mesangial cells, but proliferation of extracapillary cells may result in crescent formation. Immunofluorescence usually reveals mesangial IgA with IgG, C3, and fibrin.

Differential diagnosis

In the presence of an atypical rash other vasculitic conditions should be considered. Microscopic polyarteritis, Wegener's granulomatosis, and systemic lupus erythematosus (SLE) may all be accompanied by a crescentic nephritis. The associated clinical features with the presence of ANCA or ANA (antinuclear antibody) can help to differentiate these conditions. Cytoplasmic ANCA (C-ANCA) is more commonly associated with Wegener's granulomatosis while perinuclear ANCA (P-ANCA) is more often associated with microscopic polyarteritis. Serology is also a distinguishing feature in SLE, although ANA positive HSP has been described.[20]

Sepsis may cause a purpuric rash as may clotting disorders or thrombocytopenia. The clinical picture, particularly the distribution of the rash, with haematological investigations should identify these patients.

Treatment

The natural history of HSP is a self limiting illness in most cases. Acutely, abdominal pain and joint pain may be debilitating, and steroids have been used with some success in alleviating the abdominal symptoms.[21] Gut vasculitis may result in significant blood loss and occasionally ischaemic bowel may require resection. There is no clear evidence that treatment alters the natural history of the disease. It is, however, the significant long term morbidity associated with renal disease that has led to trials of steroids and other immunosuppressive drugs.

In 1992 Mollica *et al* reported a prospective, randomised, controlled study of steroids in the prevention of HSP nephritis.[22] Of the 221 children with HSP, 168 without nephritis at presentation were randomised to receive steroids (1 mg/kg/day) for two weeks or no steroids. None of those treated with steroids but 10 of the controls developed nephropathy within six weeks and two other controls developed nephropathy at 24 and 72 weeks, respectively. The difference in the groups was highly significant suggesting steroids have a role in preventing HSP nephritis, although even the untreated group had relatively mild involvement. In contrast, a retrospective study of 69 children with HSP of whom 50 did not have nephritis at diagnosis demonstrated a similar incidence of nephritis developing in those treated or not treated with steroids.[23] Steroids had been prescribed to manage abdominal or joint pain. More recently, in a multivariate analysis of prognostic factors for developing renal involvement in HSP, corticosteroids were found to decrease the risk, although univariate analysis showed no benefit.[24] This was a retrospective study with steroid treatment more common in patients with severe abdominal pain, which itself was found to be a risk factor for renal disease, perhaps explaining the discrepancy in these findings. In addition, persistent purpura and decreased factor XIII were significant risk factors for developing renal disease, and the authors recommended treatment with steroids for these patients.

More intensive treatment has been investigated in patients with severe nephritis. Niaudet and Habib reported a prospective study of intravenous pulsed methylprednisolone followed by oral prednisolone in patients presenting with nephrotic syndrome, > 50% crescentic nephritis, or both.[25] At 1–16 years of follow up 27 patients had clinically recovered, three had minor abnormalities, four had persistent nephropathy, and four had end stage renal failure. Comparison with historical data showed an improvement in outcome with this treatment. Oner *et al* described 12 patients presenting with rapidly progressive glomerulonephritis of whom nine had renal biopsies demonstrating crescentic glomerulonephritis (60–90% crescents).[26] These patients were treated with methylprednisolone, oral cyclophosphamide, dipyridamole, and prednisolone. There was a good response in 11 patients—complete response in seven and partial response in four—while one had a persistently decreased glomerular filtration rate. The follow up of

these patients was relatively short, from 9–39 months. A similar study of patients with ISKDC grade IV or V HSP nephritis with a longer follow up of 7.5 (0.9) years also suggested benefit from intensive treatment.[27]

Plasma exchange is used in the management of some adults with vasculitis and idiopathic rapidly progressive nephritis. There are few data in children, and controlled, prospective trials would be difficult to do because of the small numbers and disease variability. Plasma exchange has been reported in children with rapidly progressive nephritis or cerebral vasculitis associated with HSP.[28] In this retrospective study 17 patients, of whom 14 had severe renal involvement (30–100% crescents or dialysis dependent) associated with HSP and three had cerebral vasculitis, were treated with plasma exchange with combinations of steroids, cyclophosphamide, and azathioprine. All three patients with cerebral disease recovered. All nine patients with renal disease treated within a month of presentation responded and have sustained improvement whereas five of six treated later in the course of the disease developed end stage renal failure. It has previously been reported that the presence of fibrous crescents as opposed to cellular crescents is a poor prognostic factor in the outcome of crescentic nephritis, implying that a longer duration of disease has a worse prognosis.[29]

Prognosis

The long term morbidity of HSP is predominantly associated with renal involvement. In 1988 Stewart *et al* described an unselected group of 270 patients with HSP who were followed up over 13 years.[1] The overall prognosis was good, with < 1% mortality and 1% renal morbidity. In an earlier unselected series of 141 patients, 39 (28%) of whom had abnormal urinary sediment for a month, one developed end stage renal failure and two chronic renal failure giving an incidence of 1.5% for chronic renal impairment.[30] An extensive long term follow up of HSP nephritis included 78 patients from an initial cohort of 88 with a mean follow up of 23.4 years.[31] Of 39 who had had a nephritic or nephrotic presentation, 17 had hypertension or impaired renal function. Eighty two per cent of those presenting with haematuria with or without proteinuria were normal but two had renal insufficiency and one died. Of concern is that of the 17 patients that deteriorated overall, seven had recovered completely after a follow up of 10 years. Of the 15 patients in the worst clinical outcome group, five died and six had 11 transplants. Overall those with a severe clinical course and the most abnormal renal biopsy had the poorest outcome, but significant deterioration did occur in some without these poor prognostic indicators. This review also identified 24 women who had 44 liveborn infants at term. Significantly, 16 of these pregnancies were complicated by proteinuria or hypertension indicating the particularly close surveillance that is required in pregnant women.

Predicting the patients that are at risk of long term complications remains difficult. In an attempt to define risk factors Bunchmann *et al* reviewed 16 patients that developed end stage renal failure and matched them with a group of children whose creatinine clearance had returned to normal at 10 year follow up.[32] A creatinine clearance of > 125 ml/min/1.73m^2 at three years predicted recovery while a creatinine clearance < 70 ml/min/1.73m^2 predicted progression to end stage renal failure. Gross haematuria was more frequent in the group that progressed.

There is debate as to the risks of recurrence of HSP in transplanted kidneys. The rate of isolated histological recurrence—that is, without a change in urinalysis or renal function, varies from 0–89%. In a review of 78 renal transplants in both adults and children there was histological recurrence in about 50%. Clinical recurrence occurred in 20%, graft failure in 12%, and graft loss in 9%.[33] Delaying transplantation by six months to a year does not necessarily prevent recurrence. There is some suggestion that live related transplants have a higher risk of recurrence, possibly owing to a familial predisposition to the condition.

Although the incidence of significant long term morbidity in unselected series is only 1–5%,[1 34] HSP has been reported to account for between 5% and 15% of patients entering end stage renal failure.[5 32] Treatment with intensive regimens should be reserved for patients with significant renal disease associated with a crescentic nephritis or children with severe neurological involvement. However, a further prospective study of the use of an early short course of steroids in all patients with HSP would help to confirm or refute the view that steroids can ameliorate the long term outlook. It has been demonstrated that those with the most severe acute clinical and histological findings have the highest risk of long term renal impairment. However, in view of the unexpected late deterioration in some patients, long term follow up must be recommended for all who develop nephritis.

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