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Henoch-Schönlein Purpura in children

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Abstract

Henoch-Schönlein purpura (HSP) is an IgA-mediated systemic small-vessel vasculitis with a predilection for the skin, gastrointestinal tract, joints, and kidneys. Approximately 75% of cases occur in children aged between 2 to 11 years, with a peak incidence at 4 to 7 years. The diagnosis should be based on the finding of palpable purpura in the presence of at least one of the following criteria: diffuse abdominal pain, arthritis or arthralgia, renal involvement (hematuria and/or proteinuria), and a biopsy showing predominant IgA deposition. Most cases are self-limited. The average duration of the condition is 4 weeks. Recurrences are reported in up to 33% of patients. Therapy consists of general and supportive measures as well as treatment of sequelae of the vasculitis. Oral steroids may be considered for patients with severe gastrointestinal involvement. Unfortunately, early steroid treatment does not reduce the incidence and severity of nephropathy in patients with HSP.

Key words Henoch-Schönlein purpura, IgA deposition, vasculitis, palpable purpura, abdominal pain, arthritis or arthralgia, hematuria, proteinuria

INTRODUCTION

Henoch-Schönlein purpura (HSP) is an IgA-mediated systemic small-vessel vasculitis with a predilection for the skin, gastrointestinal tract, joints, and kidneys.[1] The hallmark is apressure - orgravity - dependent nonthrombocytopenic purpuric or petechial rash.[1] Abdominal pain, arthritis, and nephritis are common.[1] The condition was first described by William Heberden in 1802 who reported a 5-year-old boy with arthralgia, hematuria, abdominal pain, melena and "bloody points" over his legs.[2] In 1837, Johann Schönlein described the association of purpura and arthralgia.[3] In 1874, his former student Edward Henoch described purpura, abdominal pain, and melena as a syndrome and in 1895 went on to recognize renal involvement in this syndrome.[4,5] The syndrome now bears the names of both Henoch and Schönlein.

EPIDEMIOLOGY

HSP is the most common form of systemic vasculitis in children.[6] The incidence is 10 to 14 cases per 100,000 children per year.[7] Approximately 75% of cases occur in children aged between 2 and 11 years, with a peak incidence at 4 to 7 years.[8] The condition is twice as prevalent in boys as in girls.[6,9] HSP occurs throughout the year, but most patients present from fall to spring.[6] The condition is more common among Asians than Caucasians.[7] African-Americans are rarely affected.[10]

ETIOPATHOGENESIS

HSP is the result of a leukocytoclastic vasculitis mediated by an antigen-stimulated increase in levels of IgA, subsequent deposition of IgA antigen complexes in the vasculature of involved organs, and activation of complement pathways which leads to neutrophil accumulation resulting in inflammation and vasculitis without a granulomatous reaction.[6,9] The IgA-mediated vasculitis might result from the interactions of multiple genes and enviromental factors, such as infections, medications, and vaccinations.[7]

There is a genetic predisposition to this condition.[10] Certain human leukocyte antigens (HLA) such as HLA-DRB1*01, HLA - DRB1*07, HLA - DRB1*011, HLA - DRB1*014, and HLA-B35 may contribute to the susceptibility.[6,7,10] In addition, mutations in the Mediterranean fever gene (*MEFV*), located on chromosome 16p13.3, which encodes pyrin could be a contributing factor.[7,11] Genetic variants in the angiotensinogen gene (*ATG*) might also be responsible.[7]

Between 60 and 75% of patients with HSP have a history of upper respiratory tract infection.[1] *Streptococcus pyogenes* is the most common infecting organism.[6,8] Other reported precipitating infectious agents include parvovirus, adenovirus, hepatitis A, B, and E viruses, Epstein-Barr virus, coxsackie virus, varicella-zoster virus, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Yersinia*, *Campylobacter*, and *Helicobacter pylori*.[12,15] Drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, thiazides, nonsteroidal anti-inflammatory drugs, clarithromycin, and cytarabine have also been implicated.[10,16] Other precipitating factors include insect bites, vaccinations (influenza, hepatitis A, hepatitis B, pneumococcus, mumps, measles, and rubella), and α-1 antitrysin deficiency.[14,17-18]

CLINICAL MANIFESTATIONS

The clinical features may be atypical at the extremes of age.[6] The severity tends to be milder in children under 2 years of age and worse in adults.[6,8]

Dermatologic manifestations

A purpuric or petechial rash in a pressure- or gravity-dependent distribution is present in almost all patients with HSP (Figure 1 and Figure 2).[1,19] The face, trunk, palms, soles, and mucous membranes are usually spared.[17] The rash is often symmetrically distributed and is the presenting sign in 50 to 70% of patients; it is usually palpable and does not blanch.[1,6,10] The eruption in children appears in crops and is characterized by its polymorphism in contrast to the eruption seen in adults which is often monomorphic.[10] Some patients have target-like lesions, with each lesion consisting of a central punctate hemorrhage surrounded by circumferential regions of pallor and hemorrhage.[1]

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Bullous lesions are rare, especially if they are hemorrhagic.[20-22]

Musculoskeletal manifestations

Arthralgia or arthritis develops in 65 to 85% of affected patients and is the presenting symptom or sign in 17 to 25% of cases.[1] The frequency of joint involvement is inversely correlated with the patient's age; younger children tend to be more frequently affected.[10] Large joints, such as the knees and ankles, are the most commonly involved, but smaller-joint and spine involvement also occurs.[6-9] The joint involvement is usually symmetrical in distribution, periarticular, and not migratory.[14] Joint symptoms are transient and do not lead to permanent disability.

Subcutaneous edema is reported in 35 to 70% of patients.[1] The edema is usually noted on the dorsa of the hands and feet but may also occur on the scalp, ears, periorbital area, and abdominal wall.[23] Rarely, subcutaneous nodules have been reported.[24]

Gastrointestinal manifestations

Gastrointestinal involvement occurs in 50 to 75% of children with HSP and may precede the onset of purpura in 10 to 20% of patients.[6,8] Abdominal pain, the most common symptom, is typically severe and colicky.[1,8] The pain is usually localized to the periumbilical or epigastric area.[10] Nausea and vomiting are common.[24] Hematemesis and melena might also occur. The gastrointestinal symptoms can be attributed to mesenteric vasculitis with resultant visceral or peritoneal purpura and extravasation of blood and interstitial fluid into the bowel wall and intestinal lumen.[10,14] Intussusception is the most common surgical complication, with an overall incidence of 3.5%.[1,25] Other gastrointestinal complications include intestinal perforation, hemorrhagic ascites, protein-losing enteropathy, acute acalculus cholecystitis, and acute pancreatitis.[14,24,26-28]

Renal manifestations

Renal manifestations develop in 40 to 50% of patients, usually within 1 to 3 months of disease onset.[6] Risk factors for renal involvement include severe abdominal pain with gastrointestinal hemorrhage, age more than 5 years at onset, persistent purpura for more than one month, scrotal involvement, elevated serum IgA, and decreased serum complement C3 levels.[29,30] Hematuria (microscopic or macroscopic) is the most common renal manifestation. Other findings include proteinuria, nephrotic syndrome, and acute nephritis with hypertension.[1] Nephropathy is more severe in children older than 8 years.[1] Persistent hematuria and proteinuria predict the development of end-stage kidney disease.[14]

Genital manifestations

Orchitis is reported in 10 to 20% of boys with HSP.[6] Clinical findings, which include pain, tenderness, and swelling of the involved testicle or scrotum, can mimic testicular torsion. Epididymitis, hemorrhagic or sclerosing ureteritis, hydrocele, scrotal hematoma, scrotal edema, and labial edema have also been reported.[24,31-33]

Neurologic manifestations

Headache and behavioral changes develop in up to 31% of patients.[1,8] Seizures, visual abnormalities, verbal disability, and focal neurologic deficits are reported in only 2 to 8% of patients.[1,34] Rarely, peripheral neuropathy, facial nerve palsy, Guillain - Barré syndrome, and reversible posterior leukoencephalopathy syndrome have been reported.[34-36]

Pulmonary manifestations

Pulmonary complications include diffuse alveolar hemorrhage, interstitial pneumonia, and interstitial fibrosis.[8] In general, pulmonary complications are rare.

LABORATORY EVALUATION

There are no laboratory studies that definitively confirm the diagnosis of HSP, although an elevated serum IgA level is suggestive.[1] Laboratory studies, however, might be necessary to rule out other causes of vasculitis. Anti-neutrophil cytoplasmic antibody (ANCA) titers are normal in HSP but elevated in Wegener granulomatosis.[37]

When renal involvement is present, urinalysis may reveal dysmorphic red blood cells, white blood cells, cellular casts, or protein.[1] Elevated levels of serum creatinine or blood urea nitrogen suggest renal insufficiency associated with the glomerulonephritis of HSP. A depression in levels of serum total protein and albumin associated with proteinuria greater than 1 g/m^2/d suggests nephrotic syndrome.[1]

The hemoglobin is usually normal unless severe gastrointestinal, renal, or pulmonary bleeding occurs, in which case anemia may be noted. Leukocytosis is common. The normal

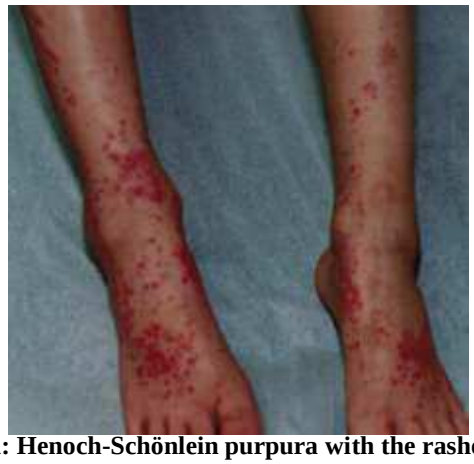

Figure 1: Henoch-Schönlein purpura with the rashes in the ankles- a pressure- or gravity- dependent distribution

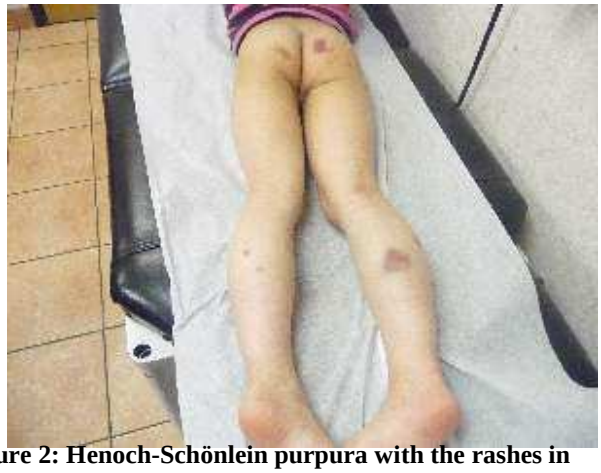

Figure 2: Henoch-Schönlein purpura with the rashes in the left leg and buttock

platelet count differentiates HSP from thrombocytopenic purpura, and normal results of coagulation studies distinguish HSP from primary hemorrhagic disorders.

DIAGNOSIS

According to the European League Against Rheumatism (EULAR) and Paediatric Rheumatology European Society (PRES), the diagnosis should be based on the finding of palpable purpura in the presence of at least one of the following criteria, namely, diffuse abdominal pain, arthritis or arthralgia, renal involvement (hematuria and/or proteinuria), and a biopsy showing predominant IgA deposition.[39] Clinically, children presenting with nonthrombocytopenic palpable purpura with multisystem (gastrointestinal tract, kidneys, joints) involvement may be diagnosed to have HSP until it is proven otherwise.

PROGNOSIS

Most cases of HSP are self-limited.[7,41] The average duration of the disease is 4 weeks except in those with persistent proteinuria or hematuria.[6] Recurrences are reported in up to 33% of patients.[6,8,40] Long-term complications are rare and include persistent hypertension and end-stage kidney disease.[6] Renal involvement is the most important prognostic factor in determining the morbidity and mortality.[14]

MANAGEMENT

Therapy consists of general and supportive measures as well as treatment of the sequelae of the vasculitis. Quiet activities (e.g. leg rest), optimal nutrition, and adequate hydration are helpful. Although, majority of patients with HSP develop renal involvement within 3 months of disease onset, they need to have extended testing of urine for a year.[14] In children with renal involvement, a low-salt diet helps minimize the possibility of hypertension. Nonsteroidal anti-inflammatory drugs such as ibuprofen can be used to relieve joint and soft tissue discomfort. Aspirin should be avoided in children.

The use of a corticosteroid medication is controversial.[6,9] It has been shown that steroids may shorten the duration of abdominal pain and may prevent major complications such as gastrointestinal hemorrhage and intussusception. As such, oral steroids may be considered for HSP patients with severe gastrointestinal involvement.[10,42] However, the use of systemic steroids must be balanced against the potential side effects.[43] A recent large scale (n = 352), randomized, double-blind, placebo-controlled trial found that early steroid treatment does not reduce the incidence and severity of nephropathy in patients with HSP.[44-45] Indications for a renal biopsy include acute renal impairment/nephritic syndrome at presentation, persistent proteinuria, rapidly deteriorating renal function, and a relapsing course.[1,41]

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