

Henoch–Schonlein purpura

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Purpose of review

The purpose of this review is to educate the reader about the one of the most common vasculitides of childhood: Henoch–Schonlein purpura. Although the disease has been described for over a century, the etiology has yet to be discovered. Adult-onset Henoch–Schonlein purpura is unusual, but through case studies, this review examines some of the common manifestations of this presentation of disease. Long-term outcome studies are still defining how this disease affects a small but significant percentage of patients afflicted with Henoch–Schonlein purpura.

Recent findings

This article will summarize recent work in molecular biology and genetics evaluating predisposing factors in the development of Henoch–Schonlein purpura. Further illustrations of the various complications of Henoch–Schonlein purpura will be reviewed. Recent long-term studies of outcomes of patients with renal disease from Henoch–Schonlein purpura will be summarized.

Summary

After reading this review, the clinician will be able to elucidate the manifestations of Henoch–Schonlein purpura, determine appropriate treatment of the disease, and, most importantly, give the patient information about long-term consequences of Henoch–Schonlein purpura.

Keywords

Henoch–Schonlein purpura, vasculitis, nephritis

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Abbreviations

GI gastrointestinal
HSP Henoch–Schonlein purpura
Ig immunoglobulin

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Henoch–Schonlein purpura (HSP) was first recognized by Heberden in 1801 and first described as an association between purpura and arthritis by Schonlein in 1837. Henoch added descriptions of gastrointestinal (GI) involvement in 1874 and renal involvement in 1899. HSP is a small vessel vasculitis whose major manifestations include arthritis, nonthrombocytopenic purpura, abdominal pain, and renal disease. In 1990, the American College of Rheumatology published diagnostic criteria for HSP. These included (1) Palpable purpura—slightly raised “palpable” hemorrhagic skin lesions, not related to thrombocytopenia; (2) Age less than 20 at disease onset—patient 20 years or younger at onset of first symptoms; (3) Bowel angina—diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea; and (4) Wall granulocytes on biopsy—histologic changes showing granulocytes in the walls of arterioles or venules. The classification further states, “For purposes of classification, a patient shall be said to have Henoch–Schonlein purpura if at least 2 of these 4 criteria are present. The presence of any 2 or more criteria yields a sensitivity of 87.1% and a specificity of 87.7%” [1]. HSP is one of the most common vasculitides of childhood and is considered to be self-limiting. One manifestation of HSP that can continue to cause lifelong problems is renal involvement [2].

Incidence of disease

Gardner–Medwin *et al.* examined the frequency and ethnic variation of childhood vasculitides in the West Midlands region of the United Kingdom [3•]. The survey was completed using monthly questionnaires sent to consultants and a single questionnaire sent to family doctors along with review of case notes with diagnostic codes for vasculitis. The annual incidence of HSP in the study was 22.1 per 100,000, which was higher than previous estimates of 13.5–18 per 100,000. The authors postulate that the potentially higher incidence of HSP may lead to an increased incidence of renal disease and a need for renal services. However, the study did not investigate if there was indeed a higher or lower incidence of renal disease in this population [3•].

Features of HSP in Thailand were reviewed, and the authors found that of 47 children with HSP, renal involvement was detected 6 months after diagnosis in six of 22 cases of children who ultimately had renal disease. This time to presentation and diagnosis of renal disease was 2 to 3 months longer than has previously been reported. All other manifestations of the disease were similar to other groups [4].

Etiology

Since the etiology of HSP is unclear, there are several case reports of associations of HSP with other illnesses. In children, rheumatic fever has been reported in association with HSP [5]. A study from Japan identified group A strep antigens on glomeruli of some patients with HSP nephritis [6]. Siblings with HSP following infectious mononucleosis are described, although one of these siblings had hematuria before the HSP, leading the authors to conjecture a genetic predisposition to the disease [7]. The association between HSP and Tuberculosis is described [8]. Colitis [9] and GI lesions [10] have also been associated with HSP

Nitric oxide production in children with HSP was studied by measuring serum nitrate levels and urinary nitrate excretion. These levels were found to be elevated in children with HSP, but the significance of this finding remains uncertain [11]. GI mucosal immunoglobulin A (IgA) deposition was noted in HSP, showing the continued role of IgA mediation in the disease process as a whole [12].

Antiendothelial cell antibodies (AECAs) were measured in 20 children with HSP, ten children with JRA for inflammatory illness matched controls, and ten healthy controls. IgG and IgM AECAs were no different in any of the groups, but IgA AECAs were undetectable in the control groups and elevated in the children with HSP [13].

Interleukin 1 receptor antagonist gene polymorphisms and their role in HSP were investigated. The serum of 96 patients with HSP or cutaneous leukocytoclastic vasculitis was examined, and an association of the polymorphism with renal involvement, but not with GI involvement, was noted [14•].

In adults, HSP was noted to be associated in one 41-year-old man with paroxysmal nocturnal hemoglobinuria. The authors speculate that a single bacterial infection triggered both of these conditions in this patient. [15]. Hepatitis C was diagnosed incidentally in a 63-year-old male with HSP [16]. A 41-year-old woman with HSP and subacute bacterial endocarditis (SBE) is also described [17].

HLA B subtypes may play a role in renal disease and HSP. In a retrospective study of 48 patients, including 11 adults, there was no increase in HLA B subtypes of the patients compared with controls. However, if only the patients with renal diseases are considered, there are significant increased frequencies of HLA B35 noted—ten of 31 patients [18].

Variations on presentations (Henoch–Schonlein purpura gone bad)

HSP is classically considered a mild vasculitis that is treated with supportive care in the outpatient setting. However, there are rare but life-threatening complica-

tions in patients with HSP. These complications are often reported as case reports.

Hemorrhagic complications of HSP are rare, but well documented. Two separate case reports of cerebral hemorrhage are included in this review. Both report girls, one almost 7 years old and the other 8 years old with cerebral hemorrhages. In the Japanese report, the patient developed blindness and loss of consciousness 2 weeks into her illness while hospitalized. The child recovered with only a homonymous hemianopia in the lower quarter of her left visual field [19]. In the Italian report, the child developed severe headache followed by tonic clonic seizures and loss of consciousness. This child recovered with no neurologic sequelae [20]. Pulmonary hemorrhage was reported in a 9-year-old female 10 days into the disease. This complication completely resolved with treatment of steroids and cyclophosphamide [21]. A 5-year-old boy was reported to have bilateral subperiosteal orbital hematomas with his HSP. He presented with bilateral exophthalmus and bilateral upper eyelid ecchymosis. Computed tomography showed well defined, nonenhancing, bilateral superior orbital masses with no bone erosion. These physical findings resolved within 2 weeks [22]. In a 6-year-old girl with HSP and renal failure, bilateral central artery occlusion occurred, presenting with sudden loss of vision. Fundoscopic examination revealed a cherry red spot with severe retinal edema at the macular and peripapillary area of both eyes, along with disc edema and venous engorgement. This patient progressed to have cerebral vasculitis and her vision never entirely corrected [23].

Edema is a well known complication of HSP. Priapism is reported in HSP in a case report of a 6-year-old [24]. Penile involvement is further described as causing a bluish discoloration on the tip of the penis, while the penile shaft also had purpura [25]. Infantile hemorrhagic edema is described, and the question is asked whether this is a very early form of HSP or a different vasculitis altogether [26,27]. Acute abdomen is a more common complication of HSP, with serositis identified in this article [28].

Conversely, other vasculitides or rheumatic diseases may present as HSP. Monastiri *et al.* reported a 6-year-old male who presented with lower extremity purpura, abdominal pain, arthralgia, and mild proteinuria and hematuria. Five days into the illness the child developed orchitis and bloody stools. Three weeks into the disease the child developed mottling and blueness of his right leg and a thrombosis was diagnosed by arteriogram [29].

Henoch–Schonlein purpura in adults

Unusual and severe complications of HSP in adults include GI disease. A case report describes a fatal outcome in a 6-year-old male whose HSP was complicated by

infarction of the ileum and subendocardial leukocytoclastic vasculitis [30].

Just as the complications of HSP in adults are different from those in children, so too the outcomes in adults are different than in children. In a retrospective study of 250 French adults with HSP followed for a median of 14.8 years, more severe renal and extrarenal manifestation of the disease was noted as compared with childhood HSP outcome. Long-term mortality from malignancy in these patients was 27%, much higher than the expected 9% in the general population of the same age. Twenty-five percent of the patients in this study developed renal insufficiency. Risk factors identified for severe renal failure using multivariate analysis included initial renal insufficiency and proteinuria [31]. A study of renal outcomes 1 year after presentation in Finnish adults shows that proteinuria and hypertension at initial presentation may predict poorer outcome [32].

Treatment

Treatment of HSP is controversial, with the use of steroids usually reserved for patients with renal involvement. Severe renal involvement has been treated with stronger immunosuppressive drugs, and an article reviews the use of steroids and azathioprine in patients with severe renal disease. In nine patients treated, all had sustained improvement, whereas two patients treated with only steroids went on to have continued renal disease [33].

Outcomes

The long-term outcome of patients with HSP is generally considered to be very good, provided they don't have renal complications. One study, however, looked at nailfold capillaroscopy in 31 patients with HSP both at the time of diagnosis and then 16 months after clinical improvement. Abnormalities were noted in nailfold capillaroscopy of the HSP patients compared with normal controls both during the acute phase of the illness and in the follow-up studies. These abnormalities included tortuosity of the capillaries, edema, derangement of capillaries, branching of the capillary network, temporary arrest of capillary blood flow, and a granular appearance of the capillary wall. The authors interpret the results to suggest that there is evidence of a chronic persistent vasculitis that is an expression of autoimmune pathology that may continue after the clinical picture resolves [34•].

Renal involvement is by far the most persistent and debilitating complication of HSP. In a retrospective analysis of 134 children with HSP, 65 patients, or 49%, were found to have renal involvement, and 97% of these patients presented within 3 months of disease onset. Univariate analysis showed that age greater than 4 years at disease onset, severe abdominal pain with GI bleeding, persistent purpura for over 1 month, coagulation factor XIII activity of < 80%, and treatment with coagulation

factor XIII were factors associated with developing renal involvement. Multivariate analysis showed that severe abdominal symptoms, age greater than 4 years, and persistent purpura increased risk of renal involvement. Severe abdominal symptoms and decreased factor XIII activity were also associated with severe proteinuria [35••].

The long-term outcome of a cohort of 26 boys and 26 girls treated for HSP at a single hospital over a 20-year period was studied retrospectively. The mean follow-up for these patients was 24.1 years. Ninety percent of the patients were examined by a physician, and all the patients were sent a health questionnaire. The study was specifically designed to examine the long-term renal outcome of these patients, regardless of their renal status at time of disease diagnosis. Nine patients initially had no renal symptoms, and none of these went on to develop renal disease. Eighteen patients had hematuria, proteinuria, or both; thirteen of these patients were considered healthy, three had mild urinary abnormalities, and two had active renal disease at the time of the study. 20 patients of the cohort initially had nephritis, nephrosis, or both. Of these patients, nine were healthy at follow-up, four had minor urinary abnormalities, five had active renal disease, and two had end-stage renal failure with renal transplant. One of the most interesting findings of this study is that of the 14 women who had experienced one or more pregnancies, nine reported a history of proteinuria, hypertension, or both during pregnancy. The women who received renal transplants were included in this group, and both had active renal disease before pregnancy. Of the nine mothers with renal complications of pregnancy, seven of those were in the most severe onset group, but two of the nine had milder renal disease with their presentations of HSP. The recommendations of the authors based on this study is that all women with a history of HSP should be carefully monitored during pregnancy, even if they had no evidence of renal disease at the time of their HSP diagnosis [36••].

Conclusions

Although HSP has been described for well over a century, we are still struggling with determining the cause of this most common vasculitis of childhood and the best treatment for the most severe outcomes. Most children with HSP have no significant sequelae, but the ones who have renal involvement can have lifelong problems. Through review of the most recent year's literature, the continued interest in this disease, its etiology, and its outcome can be appreciated.

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