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Review

The diagnosis and classification of Henoch–Schönlein purpura: An updated review ☆

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ABSTRACT

Henoch–Schönlein purpura (HSP) is a common childhood systemic vasculitis with clinical characteristics of cutaneous palpable purpura, arthralgia/arthritis, bowel angina, and hematuria/proteinuria. HSP is identified mainly based on the above presentations. Combined with pathohistological findings of leukocytoclastic vasculitis (LCV) and IgA-immune deposits in vessel walls and/or glomeruli increase the diagnostic sensitivity and specificity. However, considering the accessibility of biopsy and some patients with atypical presentations, there are still medical unmet needs in HSP diagnosis. This article reviews the diagnosis of HSP including the aspects of classification criteria, differential diagnosis, and some laboratory findings as the biomarkers with diagnostic potential.

Contents

1. Introduction

Henoch–Schönlein purpura (HSP) is a systemic small vessel vasculitis that occurs commonly in children. The annual incidence is 13–20 per 100,000 children under 17 years old [1,2]. It is characterized by non-thrombocytopenic palpable purpura that mostly located on the dependent parts like lower extremities and buttocks, arthralgia/arthritis, bowel angina, and hematuria/proteinuria. Treatment is supportive because the disease course is usually benign and self-limited [3]. Progressive impairment of renal function, bowel perforation, and central nerve system involvement is rare but major morbidity of HSP [4–6]. Aggressive therapies with steroid and/or immunosuppressants are then indicated under such conditions.

Although this disease is not uncommon in children, the etiology and pathogenesis are still yet to be determined. Previous epidemiological studies have found striking seasonal variations in HSP, with most cases occurring in the autumn and winter. HSP has also been associated with a history of preceding infections, especially upper respiratory tract infection [1,3,7]. In addition, other characteristics of HSP include the deposition of IgA and C3 in small vessel walls, polymorphonuclear neutrophil infiltration around the vessel and in vessel walls, and

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increased serum levels of IgA and proinflammatory cytokines at the acute stage [3,8]. Combined, HSP is regarded as a specific immune-mediated entity induced by environmental factors, particularly infections.

Clinically, since there are no disease-specific laboratory abnormalities, HSP is currently diagnosed based on symptoms and signs and histopathological findings [3,9]. In this article, we reviewed and compared various diagnostic criteria of HSP. In addition, differential diagnosis of HSP and some potential biomarker that may assist in diagnosing HSP were also reviewed.

2. Diagnostic criteria of HSP

Schönlein first described HSP as triad of purpuric rash, arthritis, and abnormalities of the urinary sediment in 1837 [10]. In 1874, Henoch described the association of purpuric rash, abdominal pain with bloody diarrhea, and proteinuria [11]. Up to date, several sets of diagnostic criteria for HSP have been proposed; the detail and comparison of these different classification criteria were further reviewed and discussed as follows.

2.1. The American College of Rheumatology (ACR) criteria

In 1990, ACR first proposed criteria for identifying HSP by comparing 85 patients who had HSP with other 722 patients with other vasculitis. Four criteria were finally identified including palpable purpura not related to thrombocytopenia, age ≤20 years at disease onset, acute abdominal pain, and granulocytes in the walls of small arterioles and venules on biopsy (Table 1). A patient shall be diagnosed with HSP if at least 2 of these criteria are present. The presence of any two or more criteria yielded a sensitivity of 87.1% and specificity of 87.7% [9].

2.2. Michel's criteria

By ACR criteria, however, a patient with other vasculitis presents with non-thrombocytopenic palpable purpura and granulocytes in small vessel walls or around vessels on biopsy could be classified as having HSP without other findings. For example, hypersensitivity vasculitis (HV), a kind of leukocytoclastic vasculitis (HCV) that commonly affects adults [3]. To distinguish between HV and HSP, Michel and co-workers conducted a study comparing 93 patients with HV and 85 patients with HSP and identified 6 criteria: palpable purpura not related to thrombocytopenia, bowel angina, gastrointestinal bleeding, hematuria, age ≤20 years at disease onset, and no history of medication intake at disease onset (Table 1). They found 3 or more criteria from the above list of 6 yielded 87.1% of correctly classified HSP cases; and 2 or fewer criteria from the same list of 6 correctly classified 74.2% of HV cases [12].

2.3. Chapel Hill Consensus Conference (CHCC)

Although ACR has proposed classification criteria for HSP that would provide a standard way to evaluate patients with similar presentations, there is no strict uniform definition of this disease. In an attempt to address this problem, a consensus conference on nomenclature of systemic vasculitis was held in Chapel Hill in 1994 [13]. They finally provided a consensus for HSP definition: it is a small vessel vasculitis with IgA-dominant immune deposits, typically involves skin, gut, and glomeruli, and is associated with arthralgia/arthritis (Table 1). This definition was according to the opinion of an expert panel, but was not validated with patient data and was not intended to function as a set of classification criteria [14]. Moreover, IgA-immune vascular deposits are not specific for HSP because they are found in other vasculitis syndromes such as erythema nodosum, cryoglobulinemia, coagulopathic vasculopathies and livedoid vasculitis [15,16].

2.4. Helander's criteria

Many vasculitis like urticarial vasculitis, microscopic polyarteritis nodosa, and collagen vascular disease could be confused as HSP if one uses solely ACR criteria that do not include IgA-immune deposits within small vessels [14]. In 1995, Helander, DeCastro, and Gibson proposed their revised criteria for HSP including cutaneous IgA vascular deposits, age 20 years or younger, gastrointestinal involvement, upper respiratory tract infection prodrome, and renal biopsy showing mesangioproliferative glomerulonephritis with or without IgA deposition (Table 1). The presence of 3 or more of above 5 criteria in patients with palpable purpura and histopathological LCV yielded

Table 1
Summary of classification criteria for Henoch–Schönlein purpura (HSP) diagnosis.

Classification	Diagnostic criteria
ACR 1990 [9]	≥2 of the following: 1. Palpable purpura, not thrombocytopenic 2. Bowel angina 3. Wall granulocytes on biopsy 4. Age ≤20 years at disease onset
Michel et al. 1992 [12]	≥3 of the following: HSP; ≤2 of the following: HV 1. Palpable purpura, not thrombocytopenic 2. Bowel angina 3. Gastrointestinal bleeding 4. Hematuria 5. Age ≤20 years at disease onset 6. No history of medication intake at disease onset
CHCC 1994 [13]	Vasculitis, with IgA-dominant immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles); typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis
Helander et al. 1995 [17]	Palpable purpura, not thrombocytopenic with LCV + ≥3 of the following: 1. Vascular IgA deposition 2. Age ≤20 years at disease onset 3. Gastrointestinal involvement 4. Upper respiratory tract infection prodrome 5. Mesangioproliferative glomerulonephritis with or without IgA deposition
EULAR/PRINTO/PRES 2010 [20]	Palpable purpura, not thrombocytopenic/petechiae (mandatory) + ≥ one of the following 1. Diffuse abdominal pain 2. Histopathology: typical LCV with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits 3. Arthritis or arthralgias 4. Renal involvement (proteinuria: >0.3 g/24 h or >30 mmol/mg of urine albumin to creatinine ratio on a spot morning sample; and/or hematuria, red blood cell casts: >5 red cells per high power field or ≥2+ on dipstick or red blood cell casts in the urinary sediment)

ACR, The American College of Rheumatology; HV, hypersensitivity vasculitis; CHCC, Chapel Hill Consensus Criteria; LCV, leukocytoclastic vasculitis; EULAR/PRINTO/PRES, European League Against Rheumatism/Paediatric Rheumatology International Trials Organization/Paediatric Rheumatology European Society.

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sensitivity and specificity greater than 90% [17]. However, the skin and kidney biopsies and direct immunofluorescence staining for IgA limit their usage in clinical practice, especially for pediatric patients.

2.5. European League Against Rheumatism/Paediatric Rheumatology International Trials Organization/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria

Since the above criteria have some limitations [9,12–14,17,18], in 2005 the vasculitis working group of the PRES proposed new classification criteria for pediatric vasculitis including HSP, endorsed by the EULAR. However, these proposed modifications were mainly based on a literature review and a consensus-based process and were not validated. Therefore, EULAR, PRINTO and PRES conducted a statistical validation process in 2008, with a large-scale, web-based data collection [19]. In 2010, the EULAR/PRINTO/PRES criteria for HSP were formally published. The criteria include palpable purpura as a mandatory criterion, together with at least one of the following findings: diffuse abdominal pain, LCV with predominant IgA deposits on skin biopsy, acute arthritis or arthralgias in any joint, and renal involvement as evidenced by proteinuria and/or hematuria (Table 1). The sensitivity and specificity of these classification criteria were 100% and 87% respectively [20].

Comparing with ACR criteria, EULAR/PRINTO/PRES criteria chose histopathology showing typically LCV with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits for all doubtful cases with atypical purpura distribution. Other differences were related to the inclusion of joint and renal involvement [20]. When either set of criteria as applied to their pediatric population, EULAR/PRINTO/PRES criteria showed a better sensitivity and specificity than ACR criteria [14,20]. However, EULAR/PRINTO/PRES criteria were originally derived from data of 823 children with HSP and 356 children with other vasculitis, such criteria have not been validated in adults [19,20].

3. Differential diagnosis of HSP

HSP must be distinguished from other diseases with similar presentations (Table 2). Thrombocytopenic purpura like immune thrombocytopenic purpura can be easily identified by the detection of low platelet count. If it is difficult to decide the cause of cutaneous purpuric lesions that may be presented in other types of vasculitis such as urticarial vasculitis, cryoglobulinemia, and HV, a skin biopsy and immunofluorescence study may assist in the diagnosis [3,16,17,20]. Some rheumatic diseases might have presentation of cutaneous vasculitis [3,16,21–25]. Clinical characteristics combined with laboratory abnormalities usually provide assistance to determine the underlying diseases. Furthermore, since abdominal pain is commonly presented in HSP, the more common causes of acute surgical abdomen must be considered [3].

Table 2
Differential diagnosis of Henoch–Schönlein Purpura (HSP).

	Diseases
Thrombocytopenic purpura	
	Immune thrombocytopenic purpura
	Thrombotic thrombocytopenic purpura
Other types of vasculitis	
	Hypersensitivity vasculitis
	Urticarial vasculitis
	Mixed cryoglobulinemia
	Cutaneous polyarteritis
	ANCA-associated small vessel vasculitis
Rheumatic diseases[a]	
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Sjögren syndrome
	Mixed connective tissue disorder
	Juvenile dermatomyositis
	Antiphospholipid antibody syndrome
Others	
	Septicemia
	Disseminated intravascular coagulation
	Papular-purpuric gloves-and-socks syndrome
	Mediterranean fever
	Causes of acute surgical abdomen

ANCA, anti-neutrophil cytoplasmic antibodies.
[a] Rheumatic diseases share some symptoms with HSP such as cutaneous purpuric lesions and arthritis.

4. Biomarkers for HSP diagnosis

In HSP, the platelet count is normal or increased. A moderate leukocytosis with a left shift is noted in some patients. Antinuclear antibody is mostly undetectable, and serum levels of C3 and C4 are usually within normal limit [3]. Although some proinflammatory cytokines and chemokines are elevated at acute stage [8,26], these laboratory abnormalities are not specific for HSP but can be seen in a variety of inflammatory conditions. The presence of LCV and IgA-immune deposits on skin and/or kidney biopsies significantly increases the diagnostic accuracy for HSP [14,17,20]. However, many vasculitis and glomerulonephritis show similar histopathological findings [14–16,27].

The immune deposits in HSP are principally composed of IgA1 that predominates in serum. IgA1 is structurally different from IgA2 in the hinge region of the heavy chain, where it is rich of proline and composed of 5–6 O-linked glycosylation sites. An abnormal glycosylation of the IgA1 hinge region would occur in the context of a deficiency of galactose and/or sialic acid; such a molecule is prone to cause IgA aggregation and thus macromolecular complexes [8]. Like IgA1 in IgA nephropathy, recent studies have shown aberrant glycosylation of IgA1 in HSP patients with nephritis [28,29]. In addition to the structure of IgA1 in HSP, the search for antigenic epitopes that IgA1 binds to is another important and interesting issue to be addressed. A variety of IgA autoantibodies have been found associated with HSP including IgA rheumatoid factor [30], IgA anticardiolipin antibodies [31,32], and IgA antiendothelial cell antibodies [33,34]. Recently, we found IgA1 of HSP patients bound well to β2 glycoprotein I (β2GPI) and some β2GPI-derived linear peptides. These IgA anti-β2GPI antibodies were cross-reactive to endothelial cells and induced complement-dependent cell lysis [35]. Although aberrant glycosylated IgA1 and some of above IgA autoantibodies are likely to play a pathogenic role in HSP, whether they are diagnostic biomarkers for HSP needs more studies to validate.

5. Conclusion

The current diagnostic criteria have high sensitivity and specificity; most HSP patients are accurately diagnosed based on them. However, some patients have atypical presentations and biopsies are sometimes not easily obtained. Therefore, the development of less invasive laboratory tests that are of diagnostic value is needed. Clearly, the elucidation of HSP pathogenesis becomes important that may identify some disease-specific biomarkers assisting in HSP diagnosis.

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