

Literature Review:

Risk Factors Associated With Renal Involvement in Childhood Henoch-schonlein Purpura

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Keywords:Henoch-schonlein purpura,
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IgA vasculitis, Children**ABSTRACT****Context:** Henoch-Schonlein Purpura (HSP) is a significant cause of chronic renal disease in children. This review determines some risk factors associated with renal involvement in childhood HSP.**Evidence Acquisition:** Electronic databases, including Google Scholar, PubMed, and Scopus were searched using the following keywords: "Children", "Henoch-Schonlein", "Risk factor", "Renal involvement", and "IgA vasculitis". This review was designed to identify the relevant electronic studies published in the English language from December 1998 to August 2018.**Results:** This review revealed that clinically older age at presentation, persistent rash, atypical rash, rash on unusual location, and gastrointestinal bleeding were significant risk factors for renal involvement. In contrast, joint involvement was not associated with renal involvement. Among biochemical markers, high red blood cell distribution width is a risk marker of renal involvement in HSP. In contrast, peripheral blood immunoglobulin A, antinuclear antibody, anti-streptolysin O titer, erythrocyte sedimentation rate, and C-reactive protein were not associated with renal involvement. In several studies, leukocytosis, thrombocytosis, or thrombocytopenia have been mentioned as predictors for renal involvement. Still, other studies showed the white blood cell count or platelet count are not risk factors. The effect of corticosteroids as a predictive factor of renal involvement in HSP is challenging and controversial. Furthermore, their impact was dose-dependent.**Conclusions:** Demographic factors, clinical features, and some abnormal laboratory findings are significant predictive factors for renal involvement in HSP.

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1. Context

IgA vasculitis (IgA vasculitis), previously named Henoch-Schönlein Purpura (HSP), is a leukocytoclastic vasculitis with the deposition of IgA immune complexes in small vessels. It mainly affects capillaries, venules, or arterioles (1, 2). According to the European League Against Rheumatism, the Pediatric Rheumatology International Trials Organization, and the Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) criteria, HSP should be diagnosed based on the presence of petechia or purpura (mandatory) with lower limb predominance, without coagulopathy or thrombocytopenia plus at least one of the following criteria: Gastrointestinal (GI) involvement, histopathology (IgA deposition), arthritis or arthralgia, or renal involvement (3).

Renal involvement is the most serious long-term complication of HSP. Based on EULAR/PRINTO/PRES criteria, HSP nephritis is defined as proteinuria: >0.3 g/24 h, or $\geq 2+$ on dipstick and hematuria: red cell casts; urine sediment showing >5 red cells per high-power field or red cell casts (3). Additional symptoms include fever, scrotal involvement in boys, and rarely pulmonary, neurologic, or cardiac manifestations. It has a male predominance male-to-female ratio of 1.5:1 and typically affects children aged 3 to 15 years (4). To date, the HSP etiology has remained unknown, but a possible link between genetic predisposition and environmental factors such as infectious agents, insect bites, vaccines, drugs, or food allergens are considered for the pathogenesis of HSP (5-9). In a systematic review, renal involvement occurred in 34% of children. If the kidney gets involved, it happens early—in 4 weeks in 85% and 6 months in nearly all children (10).

Gastrointestinal symptoms occur in approximately one-half of children with Ig AV (HSP) and range from mild (nausea, vomiting, abdominal pain) to more significant complications (gastrointestinal bleeding, intussusception, and bowel perforation). The guaiac-positive stool in complicated patients is typical, but massive gastrointestinal bleeding is rare (11).

To date, HSP treatment has remained primarily supportive with the maintenance of adequate hydration, nutrition, and electrolyte balance. Still, corticosteroid treatment is commonly used in the acute phase of HSP, particularly for renal and GI involvement. Cyclophosphamide, azathioprine, cyclosporine, and plasmapheresis have been used in patients with different results (12-19). Although HSP is usually a self-limiting disease

with a duration of about 4 weeks, it may have a relapsing-remitting course, and rarely, when complicated, it can be fatal (20).

The risk factors associated with renal involvement in HSP are not well known. However, epidemiologic and clinical features and some abnormal laboratory findings have been suggested to have a predictive role. In this narrative review, we assessed the quality of available evidence regarding risk factors that may predict renal involvement in childhood HSP and present a summary of our results.

2. Evidence Acquisition

Electronic databases, including Google Scholar, PubMed, and Scopus were searched using the following keywords: “Children”, “Henoch-Schonlein purpura”, “Risk factors”, “Renal involvement”, “Gastrointestinal involvement”, and “IgA vasculitis”. This review was designed to identify the relevant electronic studies published from December 1998 to August 2018. Among potentially relevant records, a total of 19 articles were selected. All papers included in this narrative review were in the English language.

3. Results

Nineteen articles were about risk factors of renal involvement in HSP. Table 1 presents the data extracted from each article by authors, year of publication, and study place. In these articles, we evaluated the risk factors of renal involvement in HSP. These risk factors are separately discussed below.

Age

There have been reports of different opinions about whether age can serve as the risk factor of renal involvement or not. There are research studies that consider age ≥ 6 years, ≥ 8 years, and ≥ 10 years as the independent clinical risk factor of HSP renal involvement. This review suggests that the older age at onset was one of the significant risk factors of renal involvement in HSP (21-25, 27).

Gender

There have been some different reports about the effect of gender on renal involvement in HSP. Most studies agreed that gender was not a risk factor for renal involvement. In contrast, Elmas AT et al. reported a male preference, and Kilic BD et al. reported a female preference in sex ratio (21, 24, 28-35).

Table 1. Assessment of risk factors of renal involvement in HSP

Authors	Year of Publication	Place of Study	Population Data	Duration of Follow-up	Risk Factors
Ma et al. (21)	2017	China	HSP: 250 HSPN: 103	One year	Age, rash duration, GI involvement, WBC, PLT, gender, joint involvement, ESR, CRP
Youying et al. (22)	2014	China	HSP: 535 HSPN: 267	Six months	Age, site of rash, GI involvement, joint involvement, WBC, PLT, ESR, Ig A
Reni et al. (23)	2014	Indonesia	HSP: 128 HSPN: 28	Retrospective study	Age
Yong-Li et al. (24)	2015	China	HSP: 141 HSPN: 45	Retrospective study	Age, obesity, duration of rash, gender, joint involvement, GI involvement, ASO, ANA, ESR, CRP, PLT
Shin et al. (25)	2006	Korea	HSP: 206 HSPN: 78	Retrospective study	Age, gender, GI involvement, persistent purpura, WBC, PLT, CRP, IgA
Sano et al. (26)	2002	Japan	HSP: 134 HSPN: 65	Retrospective study	Age, GI involvement, joint involvement, persistent purpura, steroid use
Wang et al. (27)	2018	China	HSP: 2731 HSPN: 844	Retrospective study	Age, CNS involvement
Wang et al. (28)	2016	China	HSP: 131 HSPN: 37	Three years	GI involvement, scrotal involvement, age, gender, CRP, IgA
Chang et al. (29)	2005	China	HSP: 261 HSPN: 53	Retrospective study	GI involvement, joint involvement, CNS involvement, gender
Rigant et al. (30)	2005	Italy	HSP: 94 HSPN: 17	Two years	GI involvement, gender, persistent rash, site of rash, WBC, ESR, CRP, IgA
Xu et al. (31)	2017	China	HSP: 669 HSPN: 256	Retrospective study	Age, gender, joint involvement, GI involvement, WBC, ESR, CRP, RDW, PLT
Kaku et al. (32)	1998	Japan	HSP: 194 HSPN: 65	Two years	Age, persistent purpura, gender, GI involvement, joint involvement, steroid use
Buscatti et al. (33)	2018	Brazil	HSP: 296 HSPN: 139	15 years	Gender, GI involvement, joint involvement, CNS involvement, steroid use
Elmas et al. (34)	2016	Turkey	HSP: 107 HSPN: 28	Six months	Gender, scrotal involvement, joint involvement, PLT, WBC, ESR, CRP, IgA
Anil et al. (35)	2019	Turkey	HSP: 430 HSPN: 192	One year	Age, gender, CNS involvement, GI involvement, joint involvement, steroid use, WBC, ESR, CRP
Jauhola et al. (47)	2010	Finland	HSP: 223 HSPN: 102	Six months	Age, GI involvement, gender, joint involvement, scrotal involvement, ESR, CRP, IgA
Limpongsanurak et al. (48)	2011	Bangkok	HSP: 167 HSPN: 11	One year	GI involvement, joint involvement, ASO, corticosteroid use
Beltinge & Belde (49)	2018	Turkey	HSP: 186 HSPN: 28	34 month	Age, gender, GI involvement, skin location, scrotal involvement, ASO, CRP, IgA
Parvaneh et al. (57)	2015	Iran	HSP: 69 HSPN: 6	Ten years	Steroid use

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GI: Gastrointestinal; WBC: White Blood Cell; PLT: Platelet; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; Ig A: Immunoglobulin A; ASO: Anti-Streptolysin O; ANA: Anti-Nuclear Antibody; HSP: Henoch-Schonlein Purpura; HSPN: HSP Nephritis; RDW: Red Blood Cell Distribution Width; CNS: Central Nervous System.

Skin

The presence of palpable purpura is characteristic. This rash is most prominent on the dependent or pressure-bearing surfaces, especially the lower extremities and buttocks, but it may occur in other areas (3). There have been several distinct skin rash issues, such as persistent rash, location of the rash, and atypical rash.

In two-thirds of children, HSP runs its entire course within 4 weeks after onset, but in others, purpura persists for one month or more, which is defined as persistent purpu-

ra. We found that persistent purpura was associated with HSP Nephritis (HSPN) (21, 24-26, 30, 32, 33).

Clinically, purpura on the lower limbs occurs in all patients with HSP, but a small percentage also have purpura on the face, neck, or upper limbs, and this was a significant risk factor for nephritis. So, HSP lesion location might be predictive of renal involvement and might be critical for risk stratification and treatment planning (22, 36).

Skin rash is the most common first manifestation of HSP, followed by gastrointestinal and joint symptoms. But some

HSP patients exhibit skin lesions after 24 hours of presentation, defined as atypical cases, in which GI and joint involvements appear before the skin lesions. In this review, we found that the atypical presentation of skin rash can increase the risk of developing renal involvement (35).

GI involvement

Abdominal pain, nausea, vomiting, or bleeding occurs in 51-74% of patients (11, 37-41), and 42% have severe abdominal pain (42). In 12-19% of cases, abdominal pain was the presenting symptom (38, 39). The pain is characteristically colicky. It worsens after meals (11). The abdomen may have tenderness or resemble an acute abdomen, leading to unnecessary surgery. GI bleeding occurs in 18-52% of patients with HSP (11, 37, 39, 40, 42). Bleeding is usually mild but may occasionally become severe enough to require endoscopic or surgical therapy (43-45). Among the mentioned complication, digestive tract hemorrhage is a high-risk factor for renal involvement (21, 22, 26, 28, 29, 32, 33, 35).

Joint involvement

The joint manifestations included arthritis and arthralgia. The incidence of joint involvement in HSP patients may be as high as 78% (3). Joint involvement is the second most common feature after skin manifestations (35, 46). Based on the studies in our review, in contrast to GI involvement, joint involvement is not a risk factor for renal involvement in HSP patients (21, 22, 24, 26, 31, 33, 34, 47, 48).

Laboratory markers

Analysis of laboratory indexes suggests that there were no differences in peripheral blood Immunoglobulin A (IgA), Anti-Nuclear Antibody (ANA), Anti-Streptolysin O (ASO) titer, Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) between two groups of HSP patients with and without renal involvement. However, different studies have been reported about the role of White Blood Cells (WBCs) and platelet in increasing the risk of renal involvement. Some studies revealed that leukocytosis, thrombocytosis, or thrombocytopenia are predictors for renal involvement; in contrast, others reported that WBC and platelet are not risk factors (21, 22, 24-26, 28, 31, 33-35, 47, 49).

Red blood cell Distribution Width (RDW) is routinely reported as a parameter of Complete Blood Count (CBC) that reflects the variability in the size of the erythrocytes in the blood. Also, RDW has been known as an inflammatory marker in various forms of inflammatory

diseases (50-52). In this review, we found that high RDW is a risk marker of renal involvement in HSP (31).

Treatment with Corticosteroid

As noted above, HSP treatment is mainly supportive, but in some cases, corticosteroids are prescribed in severe disease manifestations, for example, serious GI involvement and hemorrhage, pulmonary hemorrhage, and severe orchitis (53). There is considerable controversy in the published literature regarding the effect of corticosteroids as a predictive factor of renal involvement in HSP. Kaku et al. (32) and Mollica et al. (54) reported that corticosteroids diminished the risk of renal involvement. However, Ronkainen et al. (55) revealed that early prednisone therapy did not prevent the development of renal involvement. In contrast, Huber et al. (56) found no effect of prednisone in reducing renal involvement during 1-year follow-up. Murat Anil et al. (35) demonstrated that early use of corticosteroid (1-2 mg/kg/d) was associated with greater renal involvement; in contrast, Parvaneh et al. (57) showed that use of high dose corticosteroid (pulse methylprednisolone) would reduce renal complication. Our main study limitation is the unavailability of some information in each study, such as the periods for urinary abnormalities observed after the HSP diagnosis, time for the observed outcome, the dose of corticosteroid, and duration of their use. Further studies are needed to reveal the relationship between corticosteroid usage and renal involvement.

4. Conclusion

HSP nephritis is seen as the main reason for End-Stage Renal Disease (ESRD) among pediatric patients. Overall, HSP accounts for about 1% of patients with ESRD from all causes. Therefore, early diagnosis of renal involvement plays an essential role in avoiding or delaying the occurrence of ESRD. Although epidemiological factors and clinical manifestation, and some abnormal laboratory findings, are considered to have a predictive effect, the full set of risk factors associated with renal involvement remains unclear. Therefore, further studies are needed to document a risk evaluation model for renal involvement in HSP.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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