Clinical Aspect and Outcome of Henoch-Schoenlein Purpura in Children in Relation to Renal Biopsy Pathologic Findings

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Abstract- The most common childhood vasculitis is Henoch Schoenlein Purpura (HSP). It occurs at any age peaking at around 4-6 years. The classic manifestations of HSP are skin rash, along with any from a triad of other organ system involvement, including gastrointestinal, musculoskeletal, and renal systems. Renal involvement is much more common in children than in adults. 255 HSP patients attending our tertiary referral hospital enrolled in this 10-year retrospective study from 2009 to 2019. According to our study, HSP was more common in males. Most of the patients were between 1-16 years (mean 7.04 years) old. Of these patients, only 19.22% had proteinuria, 17.25% had increased creatinine, 61.7% of patients had hematuria, 67.06 had a fever, and 69.8% had abdominal pain. 24.31% of them had bloody diarrhea. Skin and joint involvement were recorded in 44.7% and 74.9% of patients, respectively. Children affected by HSP may present with different clinical manifestations. We assessed these clinical presentations and outcomes of patients and compared them with renal pathology findings to reveal any prognostic significance of renal pathologic findings in HSP patients.

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Introduction

HSP, a non-thrombocytopenic systemic vasculitis, especially occurs in children and is characterized by leukocytoclastic vasculitis affecting small vessels through the deposition of IgA-containing immune complexes (1). Ninety percent of cases occur under the age of 10 years. It is extremely uncommon in children under 2 years. HSP is slightly more common in males (1.5:1 male: female ratio), and the incidence decreases with increasing age (2). Clinical manifestations include those related to vascular involvement, such as purpuric or petechial skin rash, abdominal pain, arthralgia, bleeding diathesis, nephritis, neurologic involvement, and pulmonary hemorrhage. Renal involvement is the most important complication of HSP and may result in end-stage renal failure. Long-term prognosis depends on the severity of renal involvement (3). The age of the patient is also considered an important factor in disease manifestation, severity, and outcome (4). Renal involvement is more common in older patients and occurs in 30-40% of children compared to 45-85% of adult patients (5). There is a potential role of genetic predilection as a prognostic finding, as HSP occurs more commonly in special geographic areas. IgA vasculitis (Ig AV) is more common in Asian populations (6). HSP usually occurs in previously healthy children, and 95 percent of patients come with a skin rash at first (7). In addition to skin findings, other manifestations include a classical triad of the musculoskeletal and renal system and gastrointestinal involvement (8). Less common but more important is the involvement of other systems like the respiratory tract and neurologic systems, which are fortunately very rare. During the acute phase, 70–‒90% of

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patients complain of signs related to musculoskeletal involvement. There may be arthralgia or true arthritis with erythema, swelling, and pain. Overall, the frequency of arthritis is much lower than arthralgia (61 to 64%) and has an oligo-articular pattern (four or fewer joints), more commonly with a predilection to the joints of the lower extremity. Feet and ankles are the most commonly involved, followed by knees, wrists, elbows, and hands (9-10). The ski rash also may be confined to the affected joints, and the edema of the skin may be so severe and even may be confused with true arthritis. In rare cases, joint involvement precedes skin manifestations. Arthritis is usually transient and does not leave any residual derangements such as joint erosions. In some cases, the GI manifestations precede skin rash some days or a week leading to clinical confusion resolved when the chrematistic rash appears. Up to 72% of patients may have GI involvement, usually presenting with severe colicky abdominal pain mimicking an acute abdomen due to bowel vascular ischemia or intussusception following severe edema (7). In acute and severe cases, there may be massive bleeding presenting as melaena or hematemesis. It may be severe and life-threatening. 22 percent of patients who weren't thought to have GI involvement have asymptomatic fecal occult blood (9). Severe GI bleeding may warrant acute immunosuppressive treatment.

Renal complication, now known as Ig AV nephritis, is usually asymptomatic, and careful screening is required to find it; it occurs in around 40-50% of patients and, in most patients, runs as mild involvement with spontaneous resolvent (11). Microscopic hematuria is the most common presentation, followed by proteinuria with no edema. Macroscopic hematuria also may occur, but it is usually short-lived and limited to the acute phase. Ig AV nephritis may present as mild trivial nephritis or severe nephritis presenting as a classic nephrotic syndrome (edema, hypoalbuminemia, and heavy proteinuria). Renal involvement is the most important problem during Ig AV as it is the sole organ involvement which may lead to long-term morbidity and mortality (12). There is some evidence suggesting that patients with severe Ig AV nephritis have more severe extrarenal symptoms during the acute phase of the disease (13). Orchiditis occurs in 14% of male patients with severe pain and swelling of the testicles (14). CNS involvement is very rare, presenting with convulsions, weakness, confusion, visual disturbances, and/or reduced consciousness level (15-16). There are many genetic and genomic studies in HSP patients to demonstrate the influence of mutations as predisposing factors and also in disease presentation patterns and, in particular, the extent and severity of renal involvement. In most studies, renal consequences received more attention as it is the only organ involvement harboring long-term problems. Genetics plays a key role in determining both the predisposition to HSP and also the severity of the disease. The genetic risk factors for acquiring the disease that has so far been identified are those that encode inflammatory pathways within the blood vessels, for example, endothelial nitric oxide synthetase (e-NOS), angiotensin-converting enzyme (ACE), interleukin 18 (IL18), chemokine monocyte protein chemoattractant protein (MCP) and transforming growth factors (TGFs) and kidney responses to inflammation and include those associated with general autoimmunity predisposition such as certain human leucocyte antigen (HLA) (17).

Materials and Methods

In this retrospective study, detailed collected data of HSP patients admitted between 2009-2019 at children medical center hospital were studied. Patient information was reviewed, and all the relevant data, including clinical symptoms, laboratory findings, and in cases with renal involvement, their renal pathologic findings on renal biopsy and treatment course and final outcome were collected and studied to find any relation between these findings. Leukocytosis is defined as WBC>10000, and elevated ESR is defined as ESR>20 mm. Renal involvements were classified as isolated hematuria, hematuria and non-nephrotic proteinuria, nephrotic syndrome, and renal insufficiency. Isolated microscopic hematuria was defined as the presence of more than five red blood cells per high-power field on the sediment collected from 10 mL of centrifuged freshly voided urine. Proteinuria is defined as up to 4 mg/m2/h in 24-hour urine collected or a protein-to-creatinine ratio of more than 0.2 in random urine. Nephrotic proteinuria was defined as proteinuria in a 24-hour urine collection demonstrating protein>40 mg/m2/h or 50 mg/kg/24 hours or protein to creatinine ratio in random urine more than 2 in children. Nephrotic syndrome is defined as nephrotic proteinuria and hypoalbuminemia (Serum albumin<2.5 g/dL) with or without edema and hyperlipidemia. Renal insufficiency (RI) was defined as the rising of plasma creatinine concentration before decreasing GFR to 90 cc/min/1.73m2. Abdominal pain is defined as abdominal discomfort with or without GI bleeding. Results of renal biopsy in patients with proteinuria and hematuria are classified as ISKDC classification. Grade I (normal or discrete alterations), Grade II (proliferative mesangial

glomerulonephritis), Grade III (proliferative mesangial glomerulonephritis with crescents in less than 50% of Glomeruli), Grade IV (proliferative mesangial glomerulonephritis with crescents in less than 50% of Glomeruli), Grade V (proliferative mesangial glomerulonephritis with crescents more than 75% of glomeruli), Grade VI (membranoproliferative glomerulonephritis). Collected data were analyzed using the SPSS software version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Released 2016). For data that were normally distributed, as assessed by Kolmogorov, the correlation between continuous variables was assessed using the Pearson correlation test. Statistical significance was assigned at $P<0.05$.

Results

In a retrospective study in a tertiary center of children's medical center, 255 patients with HSP enrolled for ten years. According to our data, HSP is more common in males (male-to-female ratio 1.4), and the age of patients was between 1-16 years. The mean age was 7 years, and it was most common between 3 to 5 years old children. 61.57% of patients had hematuria, and only 19.22% of patients had proteinuria. Hypertension was recorded in 10 patients (8.9%). Table 1 shows the sex distribution, clinical presentations, and laboratory findings of patients. Renal involvement was seen in 157 patients. All patients had hematuria. 49 (19%) of patients had proteinuria, and 16 patients had nephrotic range proteinuria biopsy done in these cases and those who had proteinuria in nephrotic range or increasing creatinine or persistent proteinuria more than 8 weeks. 35 patients had increasing creatinine and prerenal azotemia, and 9 children had increasing creatinine associated with nephritic and nephrotic syndrome, returned back to normal range after treatment. Three patients (18%) had Grade II HSP nephritis (*proliferative mesangial glomerulonephritis*) and 11 patients (68%) had Grade III HSP nephritis (*proliferative mesangial glomerulonephritis with crescents in less than 50% of Glomeruli*), and 2 patients had Grad IV (*proliferative mesangial glomerulonephritis with crescents more than 75% of glomeruli*). One patient was 9 years old, and the age of the other patients was more than 10 years (mean age 12.2±2.1). Figure 1 demonstrates the age distribution of patients. There were no significant differences in ISKDC classification among the patients with nephrotic proteinuria and hematuria plus proteinuria. Overall, the severity of renal involvement was not associated significantly with extrarenal involvement. All of our patients had some deposition of immunoglobulin A in the mesangial of glomeruli. 10 patients (68%) had co-deposition of immunoglobulins A, G, and M. Co-deposition of immunoglobulins A, G, and M and worse renal pathological findings were significantly related to disease course and severity. All patients with renal involvement received immunosuppressive drugs according to their renal pathology and continued at least for 6 to 12 months. In follow-up, all patients with renal involvement had an eventual acceptable renal function, and none of them progressed to ESRD, even though most of them had received some immunosuppressive drug regimens.

Table 1. Sex distribution clinical presentations, and laboratory findings of patients

Value			Number	Percent
Sex		Male	149	58.3
		Female	106	41.7
History and clinical findings	**Skin rash (Purpura)**		244	95.7
	Arthralgia		191	74.9
	Abdominal pain		178	69.8
	Limb edema		105	41.2
	Fever		84	32.9
	Bloody diarrhea		62	24.3
	UTI		50	19.6
	Recurrence		6	2.4
	Nephrotic syndrome		16	6.3
	Recent infections	Upper respiratory tract	103	40.1
		Urinary tract	1	0.4
Laboratory findings	**Raised serum IgA**		170	66.7
	Hematuria			61.6
	Elevated ASO titer		103	40.4
	Proteinuria		49	19.2
	Increased creatinine		44	17.3

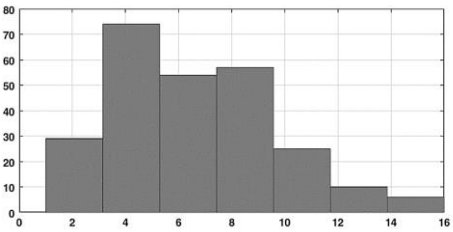

Figure 1. Age distribution of patients

Discussion

HSP is a non-thrombocytopenic systemic vasculitis of childhood affecting small vessels as a leukocytoclastic vasculitis along with the deposition of immune complexes containing IgA. The exact cause is still unknown, but the overall prognosis is very good except in cases that have renal involvement (18). The peak incidence is in 4 to 6 years old kids, but it may occur at any age. Seasonal and geographical variation in incidence implicates an environmental trigger factor. The diagnosis is a clinical one almost 95 percent of patients present with a skin rash and a triad of other system involvements, including renal, musculoskeletal, and gastrointestinal systems (19). In our study, the most common presentation was skin rash, followed by arthralgia and abdominal pain, and the last presentations were fever and renal involvement. Patients with nephrotic and or nephritic syndrome or who developed significant or persistent proteinuria underwent renal biopsy to evaluate the severity and extent of renal involvement. There are now international consensus guidelines outlining the indications of renal biopsy in these patients. In our study, 17.3% of patients had rising creatinine according to their age and sex. 19.2% of them had proteinuria, and 61.6% had hematuria. 16 children had nephrotic and/or nephritic syndrome (6.3%). So, renal involvement in our study was 61.5%. Overall, severe renal involvement and long-term problems, and renal insufficiency are more common in older patients. Renal involvement occurs in 20 to 40% of affected children (20). The risk of disease progression to renal insufficiency ranges between 5 to 15 percent of children (21). In our study, renal insufficiency occurred in 17.3% of patients, and renal biopsies were done in 16 children. The treatment plan chose according to renal biopsy findings in each case. None of the patients progressed to ESRD in the 6-12 months' follow-up period. In some studies, the severity and type of renal involvement were related to the age of the patients. Overall, renal involvement is less common in patients under 6 years old (16). In our study, all of the severe renal involvement with nephrotic nephritic syndrome or HTN or renal insufficiency were aged up to 9 years. Renal involvement is the most serious problem in HSP as it is the only organ involvement linked to long-term morbidity and mortality in both children and adult-onset HSP (12). There is evidence suggesting patients with more severe nephritis have more severe extrarenal symptoms during the acute phase of the disease specially in the background of other syndromes such as FMF (22). But, in our study severity of renal involvement didn't have any significant association with extrarenal involvement. All patients had some deposition of immunoglobulin A in the mesangium of glomeruli. As in Guo-Zhen Zhang and Mohammad Mehdi Karambin studies, the simultaneous presence of IgA, IgG, and IgM was more related to the disease course and severity of renal findings (23,24).

Renal involvement is a serious problem in HSP patients and has a higher risk of progressing to renal insufficiency, especially in pediatrics. The clinical manifestations of HSP are not always in parallel with the severity of renal findings, especially in children. Severe renal pathological manifestations are commonly associated with the co-deposition of immunoglobulins A, G, and M in renal glomeruli. More aggressive treatment and extended period of follow-up, therefore, is necessary in HSP patients with renal involvement to prevent any long-term morbidity and mortality in these cases.

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