Henoch–Schönlein Purpura Outcome in Children: A Ten-Year Clinical Study

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SUMMARY

Introduction Henoch–Schönlein purpura (HSP) is the most common vasculitis of childhood. It is characterized by symptoms including nonthrombocytopenic purpura, abdominal pain, haematuria/proteinuria, and arthralgia/arthritis. The pleiomorphism of clinical signs in HSP could be confused with other conditions or other vasculitis forms.

Objective Evaluation of HSP clinical presentation, the onset and severity of renal manifestation in affected children and their outcome.

Methods A retrospective study of 49 patients diagnosed with HSP was conducted from September 1999 to September 2009. Children with severe renal manifestations (nephrotic range proteinuria, with or without nephrotic or nephritic syndrome) have undergone kidney biopsy.

Results Twenty-five patients developed renal manifestations after onset of the disease. In our study child's older age was a risk factor for association with HSP nephritis. Six of the patients required kidney biopsy. They were successfully treated with various immunosuppressive protocols, as well as three of nine patients with nephrotic range proteinuria. Two patients developed most severe form of HSP nephritis, nephrotic-nephritic syndrome with histology grade IIIb/IVb. During the study period (average follow-up 6 years), all patients had a normal global renal function with mild proteinuria in only two cases. The prognosis of renal involvement was better than reports from other patient series.

Conclusion Long-term morbidity of HSP is predominantly attributed to renal involvement. During the study period, no patient had renal insufficiency or end stage renal disease after various combinations of immunosuppressive treatment. It is recommended that patients with HSP nephritis are followed for longer periods of time with a regular measurement of renal function and proteinuria.

Keywords: Henoch–Schönlein purpura; nephritis; children

INTRODUCTION

Henoch–Schönlein purpura (HSP) is a small-vessel vasculitis, presenting major manifestations that include arthritis, nonthrombocytopenic purpura, abdominal pain, and renal disease. American College of Rheumatology published diagnostic criteria for HSP in 1990. These criteria include palpable purpura, with slightly raised “palpable” haemorrhagic skin lesions, unrelated to thrombocytopenia, age below 20 years at disease onset, bowel angina, with diffuse abdominal pain worse after meals, or the diagnosis of bowel ischemia, usually with bloody diarrhoea, and histological changes including granulocytes in the walls of arterioles or venules [1]. The patient is considered to have HSP if at least two of these four criteria are present.

HSP is one of the most common vasculitides of childhood and is considered to be self-limiting. This systemic vasculitis (inflammation of blood vessels) is characterized by deposition of immune complexes containing IgA antibody. The exact cause for this phenomenon is presently unknown. Due to very variable clinical manifestations, it is important to exclude other more serious diseases as sepsis, other forms of vasculitides as Wegener granulomatosis, polyarteritis nodosa (PAN), systemic lupus erythematosus (SLE) and familial Mediterranean fever (FMF). The estimated annual incidence of HSP varies among studies from 14 to 22 cases per 100,000 children, with significant ethnic variation [2, 3]. One manifestation of HSP that can continue to cause lifelong problems is renal involvement [4]. Estimates of the incidence of renal involvement vary from 20% to 100%, depending on the diagnostic criteria used [5]. Renal signs are manifested in the majority of HSP patients from 3 days to 17 months after onset of the disease [6], although they can occur more frequently within the first 4 weeks [5]. Clinical expression of HSPN ranges from more common transient, isolated microscopic haematuria to nephritic syndrome, rapidly progressive glomerulonephritis and renal insufficiency [7, 8]. Although most patients experience mild and self-limited disease courses with only micro-haematuria and minimal proteinuria; some cases have more serious renal manifestations and go on to have end-stage renal disease (ESRD), accounting for 1-7% of all patients with HSP nephritis [9-12]. In selected series, HSPN leads to chronic renal insufficiency 20 years after the diagnosis in up to 20% of children. The risk of chronic renal insufficiency (CRF) is related to the initial clinical presentation. CRF is encountered in less than 5% when clinical signs at presentation are haematuria and/or minimal proteinuria, 15% when proteinuria is severe but
not nephritic or in the case of acute nephritic syndrome, 40% in the case of nephrotic syndrome, and more than 50% when nephritic and nephrotic syndrome are associated [12].

**OBJECTIVE**

In this study, we retrospectively evaluated the initial clinical presentation of HSP, the onset and severity of renal manifestation in affected children and their outcome.

**METHODS**

We conducted a retrospective study of 49 patients diagnosed with HSP at the Nephrology Department of the University Children’s Hospital in Belgrade from September 1999 to September 2009. The charts of these patients were reviewed and clinical presentations and disease courses were recorded. The diagnosis of HSP was based on the criteria of the American Colleague of Rheumatology (ACR) [1]. Nephritis was defined as the presence of gross or microscopic haematuria (>5 red blood cells per high-power microscopic field) with or without proteinuria. Children with severe renal manifestation (nephrotic range proteinuria, with or without nephrotic or nephritic syndrome) underwent kidney biopsy (six of them).

Standard histopathology examinations were performed; light microscopy and immunofluorescence staining. Glomerular changes were graded according to a classification devised by pathologists of the International Study of Kidney Disease in Children (ISKDC) [4]. Classifications of HSP nephritis are mostly based on the severity of proliferative lesions. Six histological classes are distinguished according to the presence or absence and the extension of extracapillary proliferation, with subclasses defining the degree of endocapillary proliferation. In class I only minimal changes are present, class II denotes pure mesangial proliferation without crescents, class III mesangial proliferation with <50% crescents, focal (IIIa) or diffuse (IIIb), class IV is mesangial proliferation with 50-75% crescents, focal (IVA) or diffuse (IVb), class V is mesangial, focal (Va), or diffuse (Vb) mesangial proliferation with >75% crescents, and class VI denotes membranoproliferative glomerulonephritis.

For statistical analysis of data, we used methods of descriptive and analytic statistics (t test and χ2 test). Results were analyzed by the SPSS Inc. statistical program.

**RESULTS**

In our study, the patients consisted of 30 boys and 19 girls, with ages ranging from 8 months to 15.5 years. Forty-three of them presented with first time onset of disease and other with recurrence of HSP. The mean age of the patients at the first onset of symptoms was 7.62±4.68 years. Although, HSP is the most common vasculitis in childhood, we observed that patients’ referral from primary care and other secondary paediatric centres to our tertiary facility were in 43% of cases referred under some other diagnosis, most commonly urticaria-allergic dermatitis (13%), contusion (11%), and acute appendicitis (6%). All the patients developed nonthrombocytopenic palpable purpura during the course of the disease. Joint manifestation was common during the early stages (39 of 49, 79.6%). Joints of the lower extremities, for example ankles and knees were commonly involved. Gastrointestinal (GI) tract involvement was observed in 35 of 49 patients (71.4%) with abdominal pain and apparent GI bleeding in 10 of 49 patients (20.4%) (Table 1). Only one patient with severe abdominal pain underwent surgery (appendectomy) prior to purpura onset, without intussusceptions. In our group of patients none suffered from serious CNS manifestation. Only one patient had headache which was mild and transient. Another patient presented with orchitis and had excellent prognosis. The majority of patients required no treatment (44%). We treated with corticosteroids only patients with severe GI symptomatology (38% patients with extrarenal symptomatology). According to their responses to therapy, the duration of therapy was 1-4 weeks after disease onset. The applied dose of prednisone was 0.5-1 mg/kg/body weight per day.

There were 25 of 49 patients with renal involvement or 51% of all studied patients. The interval from the onset of symptoms to the development of nephritis is summarized in Graph 1. The majority of them developed renal manifestation within a week after illness onset. Prodromal symptoms (respiratory tract infection) had 16 of 49 patients, with no difference between patients with and without nephritis (Table 2). Those patients who had renal involvement consisted of 15 boys and nine girls ranging from 3 to 15 years old. The mean age of patients was 8.96±4.02 weeks after disease onset. The applied dose of prednisone in 10 of 49 patients (20.4%) (Table 1). Only one patient underwent kidney biopsy (six of them).
had mild proteinuria. Only one patient (1%) had isolated proteinuria without haematuria. Two of 49 patients (4.1%) were diagnosed with nephrotic syndrome with presentations including heavy proteinuria, generalized oedema, hyperlipidemia, and hypoalbuminemia. Nephrotic range proteinuria was present in five of 49 patients (10.2%). One of 49 patients (2%) had nephrotic proteinuria with nephritic syndrome (2%), while two of 49 (4.1%) patients had nephrotic-nephritic syndrome. Table 2 shows that patients with HSPN had a significantly higher rate of purpura recurrence.

Kidney biopsy was done in six children; one girl and five boys (Table 3). Three of them had nephrotic proteinuria, one nephrotic proteinuria with nephritic syndrome and two of them nephrotic-nephritic syndrome. Patients with nephrotic range proteinuria had II, IIIa and IIIb grade on histology. One patient with nephrotic proteinuria associated with nephritic syndrome had IIIa grade. Two patients with nephritic-nephrotic syndrome had histologic group IIIb/IVb. Three patients with grade IIIb received MP pulse therapy in various combinations; in one patient with cyclophosphamide, in second with AZA, and in third patient triple therapy was applied; steroids, cyclophosphamide (CYCP) and mycophenolate mofetil (MM). The girl with histology grade II was treated only with ACEi (angiotensin converting enzyme inhibitor). Two patients with histology grade IIIa were treated with oral steroids and ACEi with addition of cyclosporine A (CSA) one of them. Three patients with nephrotic range proteinuria (without biopsy) treated with methylprednisolone pulse continued with prednisone during six months. Antiplatelet or anticoagulant agents were not applied in any of our patients. None of the children with HSP nephritis developed renal insufficiency or ESRD during the study period. After average period of six years of follow up, all of these patients are in remission with normal kidney function. Only two of them had mild proteinuria.

### DISCUSSION

In this study we retrospectively reviewed the initial manifestation, renal involvement and outcome of 49 HSP children at a tertiary medical centre during a 10-year period. Clinical picture of HSP is very polymorphic, and renal signs can become manifest many weeks after initial signs. This condition must be underdiagnosed initially as in our study. Almost half of admitted patients referred to our Centre with some other diagnosis. Accordingly, when based on clinical signs only, the diagnosis of HSP can be missed and some patients risk developing silent chronic renal insufficiency after decades without appropriate treatment [14]. Renal involvement, as the most important part of disease manifestation has been reported to occur in 20-50% of children with HSP [5]. Among the patients with HSP nephritis, 1-7% would suffer from ESRD [9-12]. In our series 51% of admitted children had renal involvement. The spec-

### Table 2. Clinical features between HSP children with nephritis and without nephritis

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Children without HSP nephritis (N=24)</th>
<th>Children with HSP nephritis (N=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>5.6±2.83</td>
<td>8.9±4.02</td>
<td>0.002*</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>14</td>
<td>16</td>
<td>0.687</td>
</tr>
<tr>
<td>Prodromal symptoms</td>
<td>8</td>
<td>8</td>
<td>0.689</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17</td>
<td>18</td>
<td>0.929</td>
</tr>
<tr>
<td>Bloody stool</td>
<td>4</td>
<td>6</td>
<td>0.529</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>8</td>
<td>8</td>
<td>0.079</td>
</tr>
<tr>
<td>Recurrent purpura</td>
<td>1</td>
<td>6</td>
<td>0.047*</td>
</tr>
</tbody>
</table>

*p<0.05

### Table 3. Clinical features, histology findings, applied therapy and outcome in patients with performed kidney biopsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Renal involvement</th>
<th>Proteinuria (mg/day)</th>
<th>PRT/Cr urine (mg/mg)</th>
<th>Clinical syndromes</th>
<th>OM/IF IgA</th>
<th>Therapy</th>
<th>Follow up (years)</th>
<th>Outcome GFR/PRT/Cr urine</th>
<th>Outcome (current therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>7.5</td>
<td>1 day</td>
<td>2306</td>
<td>-</td>
<td>Nephrotic proteinuria</td>
<td>IIb/++</td>
<td>MP, AZA</td>
<td>8</td>
<td>N/P</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>4.5</td>
<td>30 days</td>
<td>396</td>
<td>3.2</td>
<td>Nephrotic proteinuria</td>
<td>II/-</td>
<td>ACEI</td>
<td>5.5</td>
<td>N/P</td>
<td>ARB</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>9</td>
<td>2 years</td>
<td>-</td>
<td>5.0</td>
<td>Nephrotic proteinuria</td>
<td>IIb/+++</td>
<td>MP, CYCP, ACEI, ARB</td>
<td>6</td>
<td>N/P</td>
<td>ACEI-ARB</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>8</td>
<td>10 days</td>
<td>3656</td>
<td>4.7</td>
<td>Nephrotic proteinuria</td>
<td>IIIa/+++</td>
<td>Pronison, ACEI, ARB</td>
<td>5</td>
<td>N/P</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>12</td>
<td>10 days</td>
<td>3024</td>
<td>4.5</td>
<td>Nephrotic proteinuria</td>
<td>IIIa/+++</td>
<td>Pronison, CSA, ACEI</td>
<td>4.5</td>
<td>N/0.28</td>
<td>ACEI</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>6.5</td>
<td>7 days</td>
<td>4203</td>
<td>13.5</td>
<td>Nephrotic proteinuria</td>
<td>IIb-IVb/+++</td>
<td>MP, CYCP, MMF, ACEI</td>
<td>0.5</td>
<td>N/0.27 Microhaematuria</td>
<td>MMF, ACEI</td>
</tr>
</tbody>
</table>

PRT/Cr – proteinuria/creatinuria; OM – findings on optic microscopy; IF IgA – immunofluorescence staining on IgA; MP – methylprednisolone; AZA – azathioprine; ACEI – angiotensin converting enzyme inhibitor; CYCP – cyclophosphamide; ARB – angiotensin receptor blocker; CSA – cyclosporine A; MMF – mycophenolate mofetil; N – normal; P – physiologic; No – without therapy.
trum of renal manifestation ranged from the most frequent microhaematuria to rare cases with nephrotic proteinuria and nephrotic syndrome, and those with nephrotic syndrome combined with nephritic syndrome. During the study period none with ESRD was found. Despite a higher prevalence of HSP nephritis in our study in comparison to others (perhaps due to admission of patients only with severe onset of disease), we noticed excellent outcome of HSP nephritis. Although the aetiology of HSP is still unknown, more studies have revealed that HSP is mediated by immune system activation, which included the development of auto-antibodies against (predominantly polymorphic IgA1) endothelial cells and increased cytokines, such as TNF-α, TGF-β, IL-6 and IL-8 [15, 16, 17]. Some epidemiological studies have also shown that children with HSP usually have symptoms of upper respiratory tract infection before the onset of the disease, and most cases occurred in the autumn and winter [6]. We found a rather stable incidence during the entire year with peak in late spring. Prodromal symptoms as respiratory tract infection were found in 16 of 49 patients (32.6%), and there were no difference between HSP with or without nephritis.

In our study the average age of patients with HSP nephritis was significantly higher than in the group of HSP patients without nephritis. Kaku et al. [6] found that age at onset of more than 7 years increased the risk of developing renal involvement. Results from other groups revealed that HSP nephritis occurred more commonly in adults with clinical presentation of HSP nephritis that was severe with a relatively poor outcome, which was worse than in children [18, 19]. In addition to older age, a positive correlation between renal involvement and GI bleeding was not revealed in our study. We did not observe significant central nervous system involvement. The majority of our patients with renal involvement (60%) had a mild clinical presentation. Other patients with moderate to severe renal manifestation required immunosuppressive treatment and theoretically had a chance to develop chronic renal insufficiency [11]. In a study by Foster et al. [20], one-year treatment with oral prednisone and azathioprine in patients with moderately severe renal involvement gave positive results in comparison with historical, untreated cases. Our patients with nephrotic range proteinuria, nephrotic syndrome or combined nephrotic-nephritic syndrome were treated with various immunosuppressive regimens. Among these nine patients (18% of all patients), two of them were treated with 5 or 7 methylprednisolone pulse therapy with oral prednisone for 6 months with good clinical outcome, as reported by Niaudet et al. [21] in an uncontrolled, prospective studies of 38 children with severe form of HSPN. They suggested improvement confirmed by renal biopsy after the administration of methylprednisolone pulse therapy. There is a need for an efficient treatment for children with severe endocapillary and extracapillary proliferation and clinical presentation of nephrotic or nephritic syndrome with impaired renal function. Kawasaki et al. [22] reported that methylprednisolone and urokinase pulse therapy combined with cyclophosphamide significantly reduced urinary protein excretion and prevented any increase in crescentic and sclerosed glomeruli in HSPN patients with at least type IV, compared with methylprednisolone and urokinase therapy alone [22]. In these studies, there were no patients with persistent nephropathy or renal insufficiency among those treated with triple therapy. In our study, two most severe cases (nephrotic-nephritic syndrome) were treated with methylprednisolone and cyclophosphamide pulse therapy for 6 months, combined with mycophenolate mofetil in one of them. At most recent follow-up, there were no patients with significant proteinuria or impaired renal function. Among our six patients with severe HSPN forms, ACEI and angiotensin blocking agents (ARB) were used for treatment in three patients and mycophenolate mofetil in only one of them (after 6 months from disease onset).

CONCLUSION

HSP is the most common cause of acute vasculitis in children and seldom occurs in adults, considered to be self-limiting. Renal involvement contributes to long-term morbidity and mortality. In our study, the percentage of renal involvement was approximately 51%, which was higher than reports in some other studies [8]. During the study period, no patient had renal insufficiency or ESRD after various combinations of immunosuppressive treatment. Since this was a retrospective study, the identification of real final outcomes and risk factors of HSP nephritis were limited.

NOTE

This manuscript was presented in October, 2009 at a paediatric meeting (Days of the University Children’s Hospital) held in Sava Centre, Belgrade (23-24 October, 2009).

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Исход Хенох–Шенлејнове пурпури код деце – десетогодишње клинички испитивање

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КРАТАК САДРЖАЈ
Увод Хенох–Шенлејнова (Henoch–Schönlein) пурпура (ХШП) је најчешћи васкулитис у дејем узрасту. Клиничку слику овог облика васкултиста најчешће одликују: пурпура без тромбоцитопеније, болови у трбуху, болови и отоци зглоба, а од бубренских манифестација хематурија и протеинурија различитог степена. Проеменљива клиничка слика ХШП понекад је без забележене диференцијалне дијагнозе према другим болесним или другим облицима васкултиста. Циљ рада Циљ рада је био да се анализирају клиничка слика ХШП, појава и тежина бубренских манифестација и њихов крајњи исход.

Методе рада Урађена је ретросpektивна анализа медицинске документације свих 49 болесника са дијагнозом ХШП који су лечени на Одељењу нефрологије Универзитетске дечје клинике у Београду од јула 1999. до септембра 2009. године. Деци с тежом клиничком сликом нефритиса урађен је биопсија бубрега. Користили су се пробе протеинурије из наводних акифорних некротичних или нефритичких слипа. Резултати Код 25 деце су се после појаве болести развије буебре манифестације (неки од облика нефритиса). Старши узраст деце био је чешће удружен с појавом нефритиса. Биопсија бубрега је урађена код шест болесника. Код два болесника са најтежом клиничком сликом нефритиса (нефритско-нефритички синдром) установљен је и најтежи облик хемолитских лептица (lilb/lilb). Свих шести болесника који су подрхнути биопсији бубрега и три болесника с протеинуријом нефритског ранга лечени су различитим имуносупресивним протоколима сходно тежини клиничке слике. Током просечног периода клиничког праћења од шест година сви болесници су имали нормалну општу функцију бубрега, док је код само два болесника забележен и благ протеинурија. Прогноза лечења болесника са бубренским манифестацијама је била разнолика зависно од времена. Управо рад посвећен манифестацијама болесника са високим степеном протеинурије.

Кључне речи: Хенох–Шенлејнова пурпура; нефритис; деца

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