Henoch–Schönlein purpura – obravnava in zdravljenje slovenskih pediatričnih bolnikov severovzhodnega dela Slovenije

Henoch–Schönlein purpura: the management and treatment of paediatric patients in north–east Slovenia

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Ključne besede:
purpura Henoch–Schönlein, epidemiologija, klinična slika, obravnava, otroci.

Key words:
Henoch–Schönlein purpura, epidemiology, clinical picture, management, children.

Članek prispel / Received
17. 8. 2020
Članek sprejet / Accepted
14. 7. 2021

Izvleček

Namen: *Purpura Henoch–Schönlein je najpogostejši vaskulitis v otroški dobi z dobro prognozo. Z raziskavo primerjamo naše izkušnje z boleznijo z epidemiološkega in kliničnega stališča z raziskavami v svetovnem merilu.*

Metode: *Retrospektivno smo pregledali podatke o bolnikih s purpuro Henoch–Schönlein v obdobju med leti 2005 in 2018. Povzeli smo njihove klinične značilnosti, laboratorijske vrednosti ter zdravljenje ob prvi prezentaciji. Nadalje smo preverili, koliko, zakaj in kako smo zdravili bolnike, ki so se zaradi težav v našo obravnavo večkrat vračali. Vse navedene značilnosti smo primerjali z že objavljenimi raziskavami.*

Rezultati: *V času raziskave smo obravnavali 123 bolnikov s purpuro Henoch–Schönlein. Mediana starost*

Abstract

Purpose: *Henoch–Schönlein purpura (HSP) is the most common type of vasculitis in childhood and has a good prognosis. The aim of our study was to compare the clinical characteristics of children with HSP diagnosed in north–east Slovenia with existing data from other countries.*

Methods: *We retrospectively reviewed the data of patients with HSP in our department between 2005 and 2018, and assessed their clinical characteristics, laboratory results, and treatment at presentation. We also analysed how many patients relapsed, the causes of this, and the treatment administered. These parameters were compared with previously published research.*

Results: *During the study period, 123 patients with HSP were treated in our*

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vzorca bolnikov je bila 6,0 let (IQR 4, 9) z enakomerno porazdelitvijo med spoloma. Pri vseh je bila ob prezentaciji prisotna kožna purpura, pri 52,8 % so bile prisotne še otekline sklepov, pri 19,5 % bolečine v trebuhu in v do 10 % znaki ledvične prizadetosti. Najpogosteje smo bolnike zdravili podporno. Pri 61,8 % smo vključili nesteroidne antirevmatike, pri 13 % pa kortikosteroide. Povratnikov je bilo 15,4 %, najpogosteje zaradi ponovnih zagonov kožne purpure ter ledvičnih manifestacij.

Zaključek: *V primerjavi z raziskavami iz tujine ugotavljamo podoben vrstni red prizadetosti posameznih organskih sistemov, vendar v nižjem odstotku. V primerjavi z ostalimi raziskavami se pogosteje odločamo samo za podporno terapijo; kortikosteroide uporabljamo redkeje. V primerjavi z ostalimi raziskavami beležimo tudi manjši delež povratnikov.*

department. The median patient age was 6.0 years (interquartile range: 4–9 years) with a uniform distribution between the sexes. Along with purpura, 52.8% presented with arthropathy, 19.5% with abdominal pain, and up to 10% with renal involvement. Patients received supportive therapy the most frequently. Non–steroidal anti–inflammatory drugs were prescribed to 61.8% of patients and corticosteroids to 13%. Relapse occurred in 15.4% of patients, most presenting with skin purpura and kidney manifestations.

Conclusion: *The basic demographic data of our patients were comparable to those of other similar published studies. The order of frequency of individual organ system involvement was also similar, but the percentages were lower. Purpura–accompanying manifestations were reported less often in our study than in previous studies. Compared to other studies, supportive therapy alone was prescribed more frequently to our patients, and corticosteroids were rarely administered. Compared to other studies, a smaller proportion of patients with relapse was recorded.*

INTRODUCTION

Henoch–Schönlein Purpura (HSP) is a systemic vasculitis with small vessel inflammation and immunoglobulin A (IgA) deposition (1). It is the most frequent type of vasculitis in childhood, with an incidence of 10–30/100,000 children worldwide (2,3). In most cases, HSP is preceded by an upper respiratory tract infection, which is a possible trigger. It is assumed that HSP is the result of an irregular immune response to a pathogen (1,3).

The classic signs and symptoms of HSP include purpura, arthritis or arthralgia, abdominal pain, and kidney damage (4,5). Purpura is present in all children with HSP. Abdominal pain develops in two–thirds of patients (2,6). Renal involvement occurs in 20–55% of patients with haematuria, proteinuria, and hypertension. Other less common manifestations include cerebral vasculitis, scrotal bleeding, and interstitial pulmonary haemorrhage (2).

The diagnosis is made clinically by the presence of purpura on the lower limbs and at least one of the following: abdominal pain, arthritis or arthralgia, histological confirmation of leucocytoclastic vasculitis, or proliferative glomerulonephritis with predominant deposits of IgA immunoglobulins and kidney

involvement (2,4).

The treatment of HSP is supportive, and immunosuppression is rarely needed. Good hydration, rest, pain management, and monitoring are essential. Patients with arthritis respond well to non–steroidal anti–inflammatory drugs (NSAID). The use of corticosteroids provides a faster relief of abdominal pain and reduces the risk of intussusception (6). There is no evidence to suggest that the use of corticosteroids prevents the onset of renal disease. Immunosuppressive therapy is required in patients with HSP nephritis and severe renal involvement. Renal biopsy is recommended before commencing immunosuppressant therapy. Renin–angiotensin–aldosterone inhibitors are administered to patients with persistent proteinuria because they have been shown to reduce proteinuria and renal fibrosis (2,7).

HSP disease prognosis is generally favourable with spontaneous cessation of symptoms and signs (2). The long–term prognosis depends primarily on kidney damage (8). HSP recurs in approximately a third of patients (9).

The aim of our retrospective study was to analyse the clinical picture, course of disease, and treatment of patients with HSP in our department.

METHODS

Paediatric patients treated for HSP in the Department of Paediatrics, University Medical Centre Maribor, north–east Slovenia between 2005 and 2018 were included in the study. This department is the second largest paediatric department in the country and the only other tertiary centre besides the one in Ljubljana. Data were collected from the hospital's database. Patients were mostly managed by rheumatologists except in cases of severe abdominal pain. Patients who relapsed were seen by the same specialists working predominantly in the subspecialist field, e.g. rheumatologists, nephrologists, and gastroenterologists. The HSP diagnosis was based on clinical criteria.

We retrospectively analysed the available clinical data on the clinical picture (purpura, abdominal pain, arthritis or arthralgia, renal involvement, upper respiratory tract infection, and systolic and diastolic blood pressure) and laboratory characteristics (streptococcal test; antistreptolysin titre; occult blood in faeces; urinalysis, blood count; sedimentation rate; C–reactive protein, electrolytes [sodium, potassium, and chloride]; kidney function tests and liver damage markers; albumin; complement C3 and C4 fractions; immunoglobulins IgA, IgG, and IgM; antinuclear antibody, antibodies against cytoplasmic antigens of neutrophil granulocytes, and anti–DNA antibodies). The prescribed therapy was also analysed (supportive, NSAIDs, corticosteroids, and renin–angiotensin–aldosterone inhibitors). Finally, we assessed the number of patients who returned to our department with at least two symptom recurrences.

Statistical analysis of the data was performed using IBM SPSS Statistics Standard version 22 (IBM Corporation, Armonk, NY, USA) with basic statistical methods, e.g., the frequency of descriptive clinical characteristics, and the median with interquartile range (IQR) and minimum and maximum values for numerical parameters. Additionally, differences between boys and girls were evaluated using crosstabs, and the Pearson chi–squared text for descriptive parameters and the independent samples t–test to compare the numerical data. A p–value of <0.05 was considered statistically significant.

RESULTS

The data of 123 children (57 boys (46.3%) and 66 girls (53.7%), p=0.417) diagnosed with HSP were reviewed. Clinical and laboratory characteristics at disease onset are described in Tables 1 and 2. The median age of the children was 6.0 (IQR: 4–9). Along with purpura, more than half of the patients had signs of an upper respiratory tract infection, and a quarter had a positive streptococcal test. In more than half of cases, joint swelling occurred, while 24 patients had abdominal pain, 20 of whom had occult blood in the stools. Signs of renal involvement with haematuria or proteinuria were detected in up to 10% of patients, with normal renal function and blood pressure recorded in most cases. No significant immunological deviations were observed except for occasionally elevated IgA immunoglobulin values according to published normal values for age (10). Some of the results, e.g., electrolytes and liver

damage markers, are not shown due to their lack of relevance for this study. Blood pressure, presented in Table 2, was measured on admission. Patients with renal involvement also underwent ambulatory blood pressure measurement, which was generally within the normal limits.

At first presentation, rest and hydration were recommended to all patients, NSAIDs were prescribed in 76 children (61.8%), corticosteroids, mostly prednisone, were administered intravenously at a dose of 1–2 mg/kg or in pulses of 30 mg/kg, in 16 children (13%), and angiotensin–converting enzyme (ACE) inhibitors were prescribed for three children (2.4%). A total of 19 children (15.4%) were treated more than once, 16 (84.2%) with recurrent purpura, eight (42.1%) with kidney involvement (proteinuria, haematuria, elevated blood pressure, and mildly elevated creatinine), five with frequent joint swelling, and one with symptoms of gastrointestinal tract involvement. In 68% of relapsing patients, two or more organ systems were involved. NSAIDs were prescribed to 61.8% of patients, and corticosteroids to 13%. In addition to corticosteroids, corticosteroid pulses were administered in one patient and ACE inhibitors were used in five patients for a prolonged period (from six months to a year, or even longer).

Renal biopsy was performed in three patients. A renal biopsy was performed when laboratory and clinical data predicted the possibility of significant nephritis and the need for additional treatment, especially immunosuppressive therapy. The histopathology in all three patients showed IgA glomerulonephritis grade III according to Haas, grade III according to Lee, and M1E1S0T0 according to the Oxford classification (11). One of the patients, an active athlete, refused renal biopsy and immunosuppressive treatment. All children with kidney involvement were followed–up. At presentation, mostly low–grade haematuria and proteinuria were present. Six patients had both haematuria and proteinuria, and three had only proteinuria (0.5–1 g/day). Among the patients that relapsed, at the time of the study, only one adolescent

Table 1. *Clinical characteristics of the patients.*

Clinical manifestation	YES N (%)	NO N (%)	NO DATA N (%)
Purpura	123 (100)	0	0
Signs of upper respiratory tract infection	67 (54.4)	33 (26.8)	23 (18.7)
Positive streptococcal test	30 (24.3)	43 (35)	50 (40.7)
Joint swelling	65 (52.8)	57 (46.3)	1 (0.8)
Abdominal pain	24 (19.5)	98 (79.7)	1 (0.8)
Laboratory data	YES N (%)	NO N (%)	NO DATA N (%)
Faecal occult blood	21 (17.1)	97 (78.9)	5 (4.1)
Haematuria	11 (8.9)	111 (90.2)	1 (0.8)
Proteinuria	9 (7.3)	112 (91.1)	2 (1.6)
Positive ANA	9 (7.3)	56 (45.5)	58 (47.2)
Positive ANCA	12 (9.8)	46 (37.4)	65 (52.8)
Positive anti–DNA	0	20 (16.3)	103 (83.7)

ANA, anti–nuclear antibody; ANCA, anti–neutrophil cytoplasmic antibodies; anti–DNA, anti–DNA antibodies.

had significant proteinuria (2.7 g/day)..

There were no significant differences in clinical presentation recorded between boys and girls (data not presented). The recurrence rate was slightly higher in boys than in girls (7/57 [12.3%] vs. 12/ 66 [18%]).

DISCUSSION

The basic demographic characteristics of our patients were similar to the available global data, with a balanced gender distribution (2). The median patient age was 6.0 years, which is similar to that reported in the literature (2,12).

Along with purpura, other organ involvement occurred at the same frequency as that reported in the literature (2). Almost 10% of patients had signs of renal vasculitis. Blood pressure, monitored by sporadic measurements and ambulatory blood pressure monitoring, was normal in most patients. Otherwise, the initiation of medication was considered.

There are no specific laboratory markers for the diagnosis of HSP. Anaemia may be present as a result of gastrointestinal bleeding. Leucocytosis with elevated inflammatory parameters, due to an active respiratory infection or part of the immune response, is also common (13). The blood count of most of our patients was within the normal range. Patients showed normal kidney function tests and liver damage markers. The albumin value was very rarely checked and we did not notice any major deviations from the norm because only a few patients presented with

Table 1. *Laboratory characteristics of the patients.*

Laboratory characteristic	Number of patients	Median (IQR) (minimum–maximum)	Reference value/range	Number of patients out of range
ASLO (IU)	63	251 (IQR 499) (10–3450)	< 200	Above: 36 (57%)
Systolic pressure (mmHg)	34	113 (IQR 20) (93–189)	Age–dependent	Above: 13 (38%)
Diastolic pressure (mmHg)	34	74 (IQR 11) (62–110)	Age–dependent	Above: 14 (41%)
Leucocyte count (x 10Č9)	122	10.3 (IQR 5.0) (3.32–22.57)	Age–dependent	Above: 43 (35%) Below: 3 (2.5%)
Haemoglobin (g/L)	122	128.5 (IQR 12) (101–160)	Age–dependent	Below: 31 (25%)
Sedimentation rate (mm/h)	49	25 (IQR 27) (2–79)	> 15	Above: 33 (67%)
CRP (mg/L)	114	9 (IQR 16) (0–204)	<3	>50: 8 (7%) >3 and <50: 70 (61%) <3: 26 (23%)
Urea (mmol/L)	98	3.9 (IQR 1.3) (1.6–6.0)	Age–dependent	Below: 10 (10%)
Creatinine (µmol/L)	100	40 (IQR 19) (14–102)	Age–dependent	Above: 2 (2%) Below: 5 (5%)
Albumin (g/L)	7	34 (IQR 10) (27–44)	32–55	Below: 2 (28%)
C3 (g/L)	55	1.35 (IQR 0.32) (0.92–1.86)	0.9–1.8	Above: 1 (1.8%)
C4 (g/L)	55	0.27 (IQR 0.10) (0.11–1.43)	0.1–0.4	Above: 3 (5.4%)
Immunoglobulin IgM (g/L)	85	0.92 (IQR 0.54) (0.33–2.06)	Age–dependent	Below: 1 (1.1%)
Immunoglobulin IgG (g/L)	85	10.9 (IQR 3.8) (2.15–23.3)	Age–dependent	Above: 4 (4.7%) Below: 9 (11%)
Immunoglobulin IgA (g/L)	84	1.84 (IQR 1.21) (0.14–15)	Age–dependent	Above: 2 (2.4%) Below: 6 (7.1%)

ASLO, antistreptolysin titre; CRP, C–reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma–glutamyl transpeptidase; C3, complement fraction C3; C4, complement fraction C4.

severe renal involvement, reflected by severe protein loss or signs of compromised renal function, and even fewer presented with severe gastrointestinal manifestations. The latter can be a common cause of hypalbuminaemia in the absence of renal involvement (14). Research has shown the potential role of activation of the alternative pathway of the complement system in the pathogenesis of HSP (15). In practice, most patients have normal complement values, as observed in our patient group. Rarely, there is a transient reduction in values, which is not associated with specific complications or a worse prognosis (16). IgA immunoglobulins can be elevated in HSP, as recorded in our patients, but they are non–specific (5). Testing for antinuclear antibody, neutrophil granulocytes, and anti–DNA antibodies was performed in less than half of cases because there is no evidence in the literature that they are relevant to the pathogenesis nor do they have any clinical relevance; however, testing is occasionally performed for differential diagnostic dilemmas (5,17).

Treatment of HSP is mainly supportive (7). Therefore, NSAIDs were often prescribed with rest, hydration, and monitoring. Corticosteroids were rarely prescribed. Their use is still a matter for discussion. Some studies have shown their effectiveness primarily in the early stages of the disease (18), while others have emphasised their effectiveness in the treatment of gastrointestinal, joint, and skin symptoms (19). An increasing number of studies show that corticosteroids do not play a therapeutic role in patients with kidney manifestations, nor do they prevent the development of HSP nephritis (20).

Very rarely, in cases of renal involvement, ACE inhibitors were prescribed at the first presentation. However, ACE inhibitors play a greater role in the long–term treatment of HSP nephritis. Relapses of HSP usually occur in approximately one–third of cases, mostly with cutaneous manifestations (9,21). A smaller number of relapses was observed in our sample, which may be because patients are always alert to the possibility of relapsing purpura, which is inherently innocuous and is always followed–up by a paediatrician in primary care. Patients with relapsing purpura can usually be followed–up in primary care without referral back to the specialist care. In primary care, regular urine testing and blood pressure measurements are performed, and the development of kidney manifestations is the main indication for referral back to specialist care. The lower number of relapses may also be due to the smaller number of patients treated with severe clinical outcomes compared to other European studies (9,21,23). Nonetheless, as reported elsewhere globally (21,23), purpura relapses were most commonly recorded in our patients because of parents' concerns. This was followed by kidney manifestation, joint swelling, and gastrointestinal problem relapses, which differs from the reports in the literature, where relapses with cutaneous presentations (present in 88.7%) were followed by gastrointestinal (27.1%), renal (24.8%), and joint (16.5%) manifestations (9,21). The majority of patients who relapsed and required treatment returned because of renal manifestations, and the most commonly prescribed therapy was ACE inhibitor. These act as renoprotective agents, mostly due to their protein–lowering effect, although the also exert other positive effects (22). Patients with kidney manifestations are also followed–up for the longest period since the long–term prognosis of HSP depends on renal function (2).

A study similar to ours was carried out in Spain, where they reported a similar median patient age of 7.5 years. In 38% of patients, a prior respiratory infection was detected, whereas this was recorded in more than half of cases in our study, with positive streptococcal tests in approximately one–quarter of patients. Along with purpura, the most frequent symptoms in the Spanish study were gastrointestinal (64.5%), followed by joint impairment (63.1%) and kidney involvement (41.2%). Similar to our findings, leucocytosis was reported occasionally, along with the elevation of other inflammatory factors. However, in contrast to the Spanish study, we did not record any cases of anaemia, and we rarely recorded elevated immunoglobulin IgA values, whereas elevated serum IgA levels were observed in 31.7% of patients. Compared to our study, corticosteroids were more commonly administered in the Spanish study (35% vs. 13%), while NSAIDs were more often prescribed in our study (61.8% vs. 14%) (21).

In an Italian study, a similar average age at presentation was also reported (6.1 years). Purpura was accompanied by joint involvement in 74% of patients, kidney manifestations in 54%, and gastrointestinal manifestations in 51%. Scrotal oedema was also reported in 13% of patients. The most frequent laboratory abnormalities were an elevated sedimentation rate, elevated IgA immunoglobulins, and proteinuria. HSP relapse was reported in 35% of patients, and more frequently in patients with elevated

sedimentation rates and when corticosteroid therapy was required (23).

Other published studies on different populations with a similar age at presentation showed a relatively different clinical picture and treatment. An epidemiological and clinical study performed in South Korea reported a similar average age (6.93 years), but more frequently reported gastrointestinal tract manifestations (75%), joint (69.8%), and kidney involvement (26.9%) (24).

A similar Turkish study found a higher incidence of HSP in boys than in girls. Skin purpura was accompanied by joint involvement in 66% of patients, gastrointestinal system manifestations in 56%, and kidney damage in 30%, which is the same order as in our study, but with higher frequencies. Corticosteroids were administered to 44% of patients with abdominal pain (25), which is slightly higher than in our study, where seven out of 24 (29%) patients with abdominal pain received corticosteroids.

Our research could be further expanded by comparing the clinical picture between the paediatric and adult population, as performed by Kang et al. (26). Upper limb purpura, diarrhoea, anaemia, elevated C–reactive protein, and IgA immunoglobulins with more severe renal involvement were found to be more common in adults than in children.

The main limitation of the study is the lack of some data due to its retrospective nature.

In conclusion, the paediatric patients with HSP in our study showed similar characteristics to those reported from other countries. Purpura–accompanying manifestations appeared in a similar order of frequency to those reported in some previous studies, but were generally less commonly observed. Corticosteroid therapy was rarely administered. ACE inhibitors were more commonly prescribed in patients with kidney involvement. Those with kidney manifestations were followed–up for the longest period because the prognosis of HSP depends on the degree of renal damage.

CONFLICT OF INTEREST STATEMENT AND FUNDING

The authors have no conflicts of interest or funding to declare.

AUTHOR CONTRIBUTIONS

NMV: study design; patient data collection, follow–up, and treatment; supervised and guided the study; data revision; and manuscript revision.

MM: collected, analysed, and interpreted the data; drafted the manuscript.

All authors read and approved the final manuscript.

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