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Clinical Course of Henoch–Schönlein Purpura in South East of Iran

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Abstract

Background: The most prevalent form of systemic vasculitis in children is Henoch–Schönlein Purpura (HSP), also known as IgA vasculitis, with different manifestations. This study was performed to assess the clinical course of Henoch–Schönlein purpura in south east of Iran.

Methods: The clinical data of 221 children under age 18 years who were diagnosed with HSP at Ali Ebne Abi Taleb hospital in Zahedan, Iran, was analyzed for a ten-year period. Clinical manifestations, laboratory measures and different types of treatments were recorded from the patients' profiles with some useful additional information. Skin purpura, acute arthritis or arthralgia, gastrointestinal involvement, and renal involvement were the criteria for examination. Data description was performed by the use of SPSS 23.00.

Results: Mean age of the patients was 7.37 ± 3.19 years at diagnosis and 51.13% of them were girls. About 23.8% and 98.6% of the patients had a history of upper respiratory infections and palpable purpura, respectively. Fever was detected in 25.2% of the children. About 28.5% had vomiting and 13.6% had diarrhea. Renal involvement was observed in 130 children. During the course of the disease, 53.8% received prednisolone and 21.7% received pulse methylprednisolone due to severe GI symptoms or renal involvement. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were administered to 19.45% of the patients.

Conclusion: The patients' sex ratio was close to 1:1, though girls slightly outnumbered boys. Most HSP patients had Joint symptoms, GI symptoms and renal involvement. Arthralgias were the initial manifestations. Multicenter prospective studies with a larger number of patients are recommended to confirm the results.

Key Words: Arthralgias, Children, Clinical course, Henoch–Schönlein purpura, IgA vasculitis, Pediatrics, systemic vasculitis.

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1- INTRODUCTION

The most prevalent form of systemic vasculitis in children is Henoch–Schönlein purpura (HSP), also known as IgA vasculitis (1). Although the exact cause of HSP is unknown, a number of articles suggest that a variety of antibodies, receptors and membrane proteins, cytokines and chemokines, including TNF alpha, interleukin-6, and interleukin-8, are involved in the disease's pathogenesis (2). Additionally, some studies suggest that immune system cells, such as macrophages and lymphocytes, are primarily responsible for the expression, regulation, and production of TLR4 and TLR2, also known as Toll-like receptors. Non-immune cells like epidermal cells, fibroblasts, kidney podocytes, and mesangial cells may have also been their starting point. In this sickness, little vessels in the skin, joints, gastrointestinal parcel, and kidneys are frequently involved (2, 3). Therefore, non-thrombocytopenic purpura, arthritis/arthralgia, abdominal discomfort, gastrointestinal bleeding, and glomerulonephritis are the most typical clinical manifestations. The brain, lungs, heart, liver, and scrotum, among other organs, may occasionally be involved (4). Its prevalence, which ranges from 10 to 20 per 100,000 people per year, varies by region (5-7) for instance; the annual incidence of HSP is 17.55 per 100,000 children in southern Sweden (8), 18.60 per 100,000 children in France (9), and 55.90 per 100,000 children in Korea (10). The most prevalent age range is 5 to 10 years old, with a mean age of 6 years (5, 7), and the majority of publications indicate that HSP is more prevalent among males (2:1 ratio) and occurs most frequently in fall and winter (6). It is often clinically diagnosed and has a set of defined criteria, among which the criteria stipulate by American College of Rheumatology proposed that at least two of the following elements must be present: palpable purpura without thrombocytopenia, less than 20 years of age at the onset of symptoms; a biopsy reveals granulocytes around the arterioles or venules or bleeding in the gastrointestinal tract. EULAR, PRINTO, and PRES are additional diagnostic criteria (3, 10). Infections, particularly infections of the upper respiratory tract, medications, food, insect bites, vaccinations, and physical conditions like being exposed to the cold that causes the disease to begin are all factors that can exacerbate the condition(2). Considering the above mentioned literature, this study sought to assess the clinical significance of laboratory parameters and clinical features in Henoch–Schönlein purpura.

2- MATERIALS AND METHODS

At the Ali Ebne Abi Taleb hospital in Zahedan, Iran, we performed a retrospective analysis on the clinical data of 221 patients who were diagnosed with HSP over a ten-year period (March 2010 to December 2020). The followings were the eligibility requirements for this study: The European League Against Rheumatism, the Paediatric Rheumatology European Society, and the Pediatric Rheumatology International Trials Organization (EULAR/PRES/PRINTO) served as the foundation for the diagnostic criteria for children ranging in age from one to 18 years. The study did not include any patient who had previously been diagnosed with rheumatic, immune, hematological, or renal diseases. Skin purpura, acute arthritis or arthralgia, gastrointestinal involvement (abdominal pain, occult blood in the stool, melena, or hematochezia), and renal involvement (proteinuria or hematuria) were the criteria for examination. Commonly palpable purpura or petechiae primarily affect the lower limbs, unrelated to thrombocytopenia (which is always present), and at least one of the followings:

Acute onset of diffuse abdominal colicky pain, as determined by history or physical examination. Intussusception and gastrointestinal bleeding may occur. Joint pain or swelling that restricts movement is considered acute onset arthritis. Arthralgia: pain in the joints without swelling or limitation of movement. Renal involvement: protein >+ on dipstick or pee protein/creatinine proportion > 0.2 mg/mg on a spot morning test. Hematuria: > 5 red blood cells per high-power field in the urine sediment or less than 2+ on the dipstick. The urinary sediment is colored by the presence of red blood cells. On three occasions, hypertension (systolic and/or diastolic blood pressures below the 95th percentile for gender, age, and height) was mentioned. The patient's medical records were used to retrieve all clinical profiles and blood test results. C - reactive protein (CRP) levels, the number of White Blood Cells (WBC), neutrophils, and hemoglobin. Results of the complete blood count test were used to calculate the platelet count and the Mean Platelet Volume (MPV).

2-1. Data analysis

All statistical analyses were performed using IBM SPSS 23.0 (IBM Corp., Armonk, NY). Quantitative variables are expressed as mean ± SD and categorical variables as absolute and relative frequencies.

3- RESULTS

In the present study the recorded data of 221 children with HSP was analyzed. The results demonstrated that the mean age at the diagnosis was 7.37 ± 3.19 years, ranging from 1 to 18 years. The mean weight of children was 22.13 ± 9.91 kg, which ranged from 8.20 to 66 kg. Girls were 51.13% of the children. Autumn (42.08%), followed by winter (23.7%), summer (20.8%), and spring (14.02%), was the season with the highest rate of disease onset. Among them, 57 children (23.8%) indicated that they had a history of upper respiratory infections. All of the patients were hospitalized with the mean hospitalization of 6.30 ± 2.88 days. The mean systolic and diastolic blood pressures were 97.64± 16.31 mm Hg, and 63.96 ± 12.73 mm Hg, respectively. **Table 1** shows the clinical manifestations in children hospitalized with Henoch–Schönlein Purpura, among whom 98.6% had palpable purpura and 45.5% had arthralgia, followed by arthritis in 31.4% and then extremities edema in 38.4%. Fever was detected in 25.2% of the children.

Table-1: Clinical manifestations in children hospitalized with Henoch–Schönlein Purpura

Clinical manifestations		Frequency (N)	Percentage (%)
palpable Purpura		218	98.6
Joint symptoms	Arthralgia	110	45.5
	Arteritis	76	31.4
Abdominal symptoms	Abdominal pain	152	62.8
	Gastrointestinal bleeding	34	15.3
	Vomiting	69	28.5
	Diarrhea	33	13.6
Renal involvement	Isolated hematuria	50	22.6
	Non-nephrotic proteinuria	45	56.9
	Hematuria and non-nephrotic proteinuria	18	7.4
	nephrotic proteinuria	17	21.5

About 62.8% had abdominal pain; among them, 34(15.3%) had GIS bleeding of whom 5(2.3%), 13(5.9%) and 16(7.2%) had Upper GI Bleeding, Lower GI Bleeding and occult bleeding, respectively (**Tables 1** & **2**).

Table-2: Frequency of GI conflicts in children hospitalized with Henoch–Schönlein Purpura

Type of GI involvement	Number	Percentage
Without Involvement	187	84.6
Upper GI Bleeding	5	2.3
Lower GI Bleeding	13	5.9
Occult Blood	16	7.2
Total	221	100%

About 28.5% had vomiting and 13.6% had diarrhea. In cases of upper gastrointestinal bleeding endoscopically, one case of hiatal hernia and three cases of diffuse erythema in the duodenum were reported. In cases where colonoscopy was performed, an increase in colon thickness was seen. Renal involvement was observed in 130 children among whom 22.6%, 56.9%, 7.45% and 21.5% had isolated hematuria, Non-nephrotic proteinuria, Hematuria and non-nephrotic proteinuria, and nephrotic proteinuria, respectively (**Table1**). It is credible that among our children, those with renal involvement admitted in autumn were more frequent. The main laboratory findings are summarized in **Table 3**.

Table-3: Descriptive statistics of Laboratory measures in children hospitalized with Henoch–Schönlein Purpura

Variable	Min	Max	Mean	SD
White blood cell,× 10^{3} /µL	4200	37200	10970.77	4779.54
Seg (%)	22.60	95	61.43	13.94
Hb (g/ dl)	7.90	17.80	11.53	1.69
MCV(fl)	56.10	92.50	77.63	6.95
PLT × 10^{3} /µL	29000	910000	387000.89	149000.81
MPV(fl)	6.30	11.50	8.31	0.88
BS (mg/dL)	44	312	98.57	25.80
BUN (mg/dL)	5	56	12.92	6.45
Creatinine (mg/dL)	0.2	5	0.59	0.33
Na (mEq/L).	121	152	138.47	4.24
K (mEq/L).	3.1	6.60	4.34	0.43

Table 4 represents abdominal Ultrasonography findings in children hospitalized with HSP.

As observed in the table 133 had normal Ultrasonography and from the children with abnormal Ultrasonography, 133(60.18%), 11(4.97%), 20(9.12%), 9(4.07%), 17(7.69%), 8(3.61%), 13(5.8%) and 10(4.52%) had Normal, Increased kidney echogenicity, Abdominal Fluid, Increased kidney echogenicity and abdominal fluid, Mesenteric Adenopathy, Mesenteric Adenopathy and Fluid, Invagination, and Increased bowel loop thickness. Among the children with intussusception, 2 required surgery, and

the rest healed. Two cases of laparotomy, 3 cases of appendectomy and 1 case of bile collapse needed cholecystectomy. There were 3 children of sclerotome edema without proteinuria.

Table-4: Abdominal Ultrasonography findings in children hospitalized with Henoch–Schönlein Purpura

Variable	Number	Percent
Normal	133	60.18%
Increased kidney echogenicity	11	4.97%
Abdominal Fluid	20	9.12%
Increased kidney echogenicity and abdominal fluid	9	4.07%
Mesenteric Adenopathy	17	7.69%
Mesenteric Adenopathy and Fluid	8	3.61%
Invagination	13	5.8%
Increased bowel loop thickness	10	4.52%
Total	221	100

Table 5 demonstrates that during the course of the disease, 119 (53.8%) children received prednisolone (2 mg/kg/day) at the beginning and tapered slowly according to the patient's clinical findings. Frothy eight (21.7%) were treated with pulse methylprednisolone (30 mg/kg) due to severe GI symptoms or renal involvement. Non-steroidal anti-inflammatory drugs (NSAIDs) were administered to 43 (19.45%) children. Two (0.9%) of the children had received cyclophosphamide for renal involvement, and one (0.45%) was treated with mycophenolate mofetil because of GI bleeding.

Table-5: Different types of treatment in children hospitalized with Henoch–Schönlein Purpura

Treatment	Frequency	Percent%
Non-steroidal anti-inflammatory drugs (NSAIDs)	43	19.45 %
Prednisolone	119	53.84%
Methylprednisolone + Prednisolone	48	21.74%
Surgery	8	3.61%
Other	3	1.35%
Total	221	100

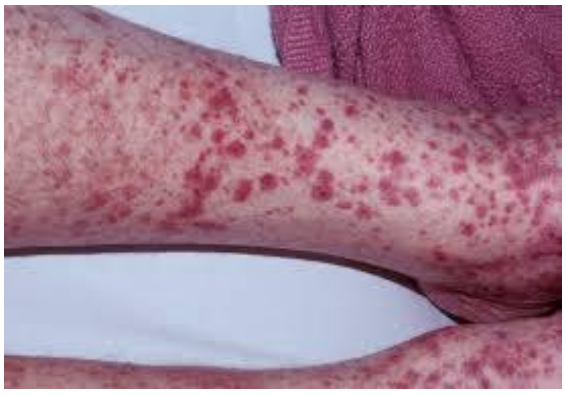

Fig. 1: The patients' skin

3- DISCUSSION

The purpose of the study was to evaluate the clinical course of HSP in children. It was found that the girls were a little more in number, but not much. Most HSP patients were seen in fall, followed by winter, summer, and spring. Around 23.8% of the patients revealed a background marked by upper respiratory contamination. 98.5% of patients had palpable purpura, 45.5% had arthralgia, 31.4% had arthritis, and 38.4% had edema. About 6.28% of patients experienced abdominal pain, 14.03% experienced GI bleeding, and 5.88% experienced intussusception. Diarrhea was the clinical manifestation with the lowest severity. About one third of the patients presented with renal involvement. Kiliç et al. (11), in a study on the risk factors for children with HSP, found that males were more prevalent and that the mean age was 7.4±2.8 years. Ekinci et al. (12) conducted a study on 214 HSP patients, with a higher proportion of males and a mean age of 7.6±3.1 years. Sano and others, (13) presumed that age of more than 4 years was an autonomous risk factor for renal inclusion, while Kaku et al. (14) found a higher risk of renal involvement in patients who were older than 7 years at the time of onset (15). Kim et al. found that children with HSP had a significant risk of renal involvement when they were female. In their study the rate of HSP was found to be higher in male patients. However, comparable with our finding, Gómez et al. (6) reported that the patients' sex ratio was close to 1:1. Their onset age was on average 7.02 years old. Children with HSP and controls had mean ages of 7.84±2.81 and 7.01±3.57, respectively. Among the impacted children, 52% were boys and 48% girls, with a sex proportion of 1.08. Abbas et al. (16) found that 52 children with HSP had an onset age of 6.76 years, with a higher proportion of girls under the age of 6 and a higher proportion of boys over the age of 6 years that is comparable to our findings only for children under the age of six. In their study, Ozturk and Çakan (17), reported that leukocytosis with neutrophilia (WBC): 10700/mm3 (4600–28000), the absolute number of neutrophils 6400/mm3 (2000–26000)] and a slight elevation of acute phase reactants (CRP: 9.6 mg/L (0.1-158), erythrocyte sedimentation rate (ESR): 22 mm/hr (5–118)] were observed when HSP was first identified. Huang et al. (18) tracked down that the proportions of BUN, Cr, and Hb were 13.3mg/dl, 0.77 mg/dl, and 13 g/dl individually. Despite the fact that the participants in Huang et al.'s study were adults, consistent with their findings in the given order, the present study found 12.92, 0.58, and 11.53. In aother study, Gökçe et al. (19) found that 18.3% of patients had WBC greater than 10000mm3 and CRP of 0.7 mg. dl. Yet another study by Ekinci et al. (12) concluded that HSP patients with severe GI involvement and biopsy-proven nephritis had a higher neutrophil count and Neutrophil-to-Lymphocyte Ratio (NLR). Furthermore, just platelet count was lower and MPV was higher in patients with repetitive HSP. Abbas et al. (16) reported that 48% of their patients had an elevated ESR and were anemic, and that 19% of them had thrombocytosis, with a mean platelet count of 2.85. In their study, 15% of patients had abnormal results in urine analysis, the majority of whom had hematuria. In the end, they discovered that 3.84 percent of patients suffered from persistent proteinuria. They also reported that purpuric rash was observed in all, arthritis in 77%, and abdominal pain in 56% of patients; and these presenting symptoms were the most common. According to Fu et al. (20), NLR was found to be an appropriate and useful biomarker for predicting gastrointestinal complications and renal involvement in HSP patients. Zhao et al. (21) conducted a study on 135 children with HSP and 86 healthy controls. Out of their patients, 77

patients had arthritis, 46 had gastrointestinal involvement and 15 had renal involvement. The most common predisposing factors were upper and lower respiratory tract infections, allergies and seasonal variation. They found that upper respiratory tract infection was the major triggering factor in 40.7% of cases. This might be due to the poor quality of air and the significant change in temperature during winter which may easily precipitate respiratory tract infections in children. Similarly, the present study found that the disease was more prevalent in autumn, followed by winter, summer and spring, respectively. The hospitalization period was around six days. There were not any seasonal differences in terms of distribution of renal involvement. The largest number of patients were admitted to hospital in autumn. Kiliç et al. (11) stated that patients with skin lesions, joint involvement, soft tissue swelling, and low Mean Platelet Volume (MPV) levels had significantly more gastrointestinal involvement. In addition, they discovered that two of the patients were operated due to intussusception (1%) and that 29.6% of the patients had abdominal pain with or without GI bleeding. Gómez et al. (6) observed that HSP typically occurs in fall and winter. More than 80% of patients had problems with their upper airways. Although the reason for occasional dissemination is obscure, it is likely connected with the activity of setting off factors, like infectious agents. In addition, this study found that joint involvement occurred prior to purpura onset in 22% of the patients with the atypical form of HSP and 78% of patients with the typical form. Common signs and symptoms were GI involvement (82 %), kidney problems (54 %), and renal contribution (19 %).

In Zhao's (21) study, the incidence of skin purpura, arthritis, GI and renal involvement among patients was 100%, 57.0%, 34.1% and 11.1%, respectively, while Alizadeh et al. (22) reported the incidence of GI in 77% of patients. Kiliç et al.,(11) stated that the most common symptom of HSP was purpuric skin rash. About 50.5% had arthritis/arthralgia, mostly in the lower extremity joints. The risk of joint involvement was 2.18 fold higher in girls, and 2.63 fold higher in patients with soft tissue edema. Kim et al. (15) showed that the patients with renal involvement had significantly higher ages at diagnosis in comparison to those without renal involvement. Kim et al. (15) found that the Odds ratio for renal involvement in pediatric HSP increased by 13% for every 1-year increase in age at onset. And female sex was another significant risk factor for renal involvement. These results are similar to those reported by Kilic et al. (11) and Demir et al. (23); and comparable with those issued by the present study. Among the patients with renal involvement in the study by Kim et al. (15), 28.4% had only microscopic hematuria, 53.7% had non-nephrotic range proteinuria, and 17.9% had nephrotic-range proteinuria during the follow-up. Ekinci et al. (12) reported that biopsy-proven nephritis was found in 7.5% of the patients. Kiliç et al. (11) proposed that the risk of renal involvement was significantly higher in girls, in patients >10 years, and in patients with elevated C-reactive protein (CRP); and about 15.1% of the patients had renal involvement. Ekinci et al. (12) also found that 36% of the patients had severe GI involvement, only 5.6% were diagnosed with symptoms, and 13.5% of patients had HSP recur. In the study by Zhang et al. (24), 36 of 88 children diagnosed with HSP, received intravenous glucocorticoids and 52 received oral corticosteroids. In another study by Breda et al. (25), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were used by 67% of patients who received drug therapy. Because of persistent skin lesions, severe abdominal pain, or scrotal involvement, corticosteroids (CS) were given 30% of the time.

Immunosuppressive treatment was expected in 2 patients with renal association, Azathioprine (AZA) and Cyclophosphamide (CYC) were the drugs chosen. Kiliç et al., (11) found that about 53.8% received prednisolone at the beginning of the course of HSP disease and tapered slowly according to the patient's clinical findings. Approximately, 21.7% were treated with pulse methylprednisolone due to severe GI symptoms or renal involvement. Non-steroidal anti-inflammatory drugs (NSAIDs) were administered to 19.45% children. Only two children received cyclophosphamide for renal involvement, and one was treated by mycophenolate mofetil because of GI bleeding. Abbas et al. (16) reported that 22 of 52 patients required steroids in addition to treatment for their symptoms. In the current study, retrospective design and the mono-clinic inclusion of children were the primary limitations. Additionally, we only assessed laboratory values during the disease's acute phase.

4- CONCLUSION

The patients' sex ratio was close to 1:1, though girls slightly outnumbered boys. The majority of HSP patients had GI involvement; and palpable purpura and arthralgia were the initial manifestations. Even in patients with a severe initial presentation, spontaneous recovery was seen. It was less common to involve the kidneys. The treatment of abdominal pain, arthralgia, and purpura with corticosteroids appears to play a role in the symptomatic management of HSP. Multicenter prospective studies with a larger number of patients are recommended to improve the results.

5- ETHICAL CONSIDERATIONS

The Declaration of Helsinki's principles were followed when conducting the study. The Ethics Committee of Zahedan University's medical sciences reviewed and approved the protocol (IR.ZAUMS.REC.1400.019).

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7- CONFLICT OF INTERESTS

None.

8- AUTHORS' CONTRIBUTIONS

Simin Sadeghi-Bojd: Supervising the study and main concepts, Literature review.

Alireza Teimouri: Data analysis, Literature review and drafting the manuscript.

Vahid sheikh: Data collection.

Khadijeh Rashidi Mehr: Data collection.

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