Henoch-Schonlein purpura in children from the eastern province of Saudi Arabia

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ABSTRACT

الأهداف: دراسة المظاهر السريرية والوبائية لفرفرية هينوخ شونلاين (الطفح الجلدي النزفي) خلال خمسة عشر عاما لدى أطفال المنطقة الشرقية من المملكة العربية السعودية.

الطريقة: تم مراجعة جميع الملفات الطبيه للمرضى الذين أصيبوا بفرفرية هينوخ شونلاين وأجريت دراسة رجعية في مستشفى الملك فهد الجامعي الخبر، المملكة العربية السعودية وذلك خلال الفترة من يناير 1996م حتى ديسمبر 2010م.

النتائج: من بين 78 مريضاً، 46 (59%) ذكور بنسبة 1.4 ذكرا لكل أنثى، وقد تراوحت أعمارهم بين 22 شهرا إلى ١٢عاما كما كان متوسط العمر 6.3 عام. رصد المرض في فصلي الخريف والشتاء عند حوالي 60% من الأطفال، كما تعرض أكثر من نصف الاطفال تقريباً للزكام والتهابات الحلق قبل ظهور أعراض المرض. وبالفحوصات المخبرية وجد ارتفاع مستضدات المكورات العقديه عند 24 (46%) مريض ممن أجري لهم هذا الاختبار. ظهر الطفح الجلدي الوصفي للمرض عند جميع الأطفال 100% أما باقي المظاهر السريريه فكانت على النحو التالي: الآم مفصليه عند 66%،أعراض هضميه 47% وتظاهرات كلويه 24% ،وذمة الصفن والتهاب الخصية عند 15% من الذكور. كان سير المرض حميدا بشكل عام باستثناء حالة واحدة كان التهاب الكلية فيها شديدا حيث ترافق مع نزف رئوي وقصور تنفسي حاد. في الوقت الذي لم يتطلب المرض سوى معالجة عرضيه وبعض المسكنات البسيطه في أغلب الحالات، تطلب وصف دواء الاستيروئيد لأحد عشر مريضا (14%). تم وبفضل الله شفاء جميع المرضى بإستثناء حالة فرط توتر شرياني لمريض عانى من إلتهاب كليه حاد في بداية المرض. سجلت ٦ حالات انتكاسة للمرض (7.7%) خلال فترة امتدت بين شهر إلى سنتين من الشفاء التام.

خاتمة: أظهرت هذه الدراسة أن فرفرية هينوخ شونلاين في المنطقة الشرقية من المملكة العربية السعوديه مرض حميد بشكل عام،ولا يوجد أي اختلاف إحصائي في مظهره السريري والوبائي عن المناطق والبلدان الأخرى .

Objectives: To evaluate the epidemiological and clinical profile of children with Henoch-Schonlein purpura (HSP) in eastern Saudi Arabia during a 15-year period.

Methods: The medical records of children discharged with a diagnosis of HSP from King Fahad Hospital of the University, Al-Khobar, Saudi Arabia, between January 1996, and December 2010, were reviewed retrospectively.

Results: Of 78 patients, 46 (59%) were boys, with a male to female ratio of 1.4:1. The patients' ages ranged from 22 months to 12 years, with a mean of 6.3 years. Approximately 60% of cases were presented during autumn and winter. Upper respiratory tract infection preceded HSP in over half of the patients and antistreptolyzin O (ASO) titer was positive in 11 of the 24 (46%) children tested at presentation. The main clinical features included skin purpura (100%), arthritis or arthralgia (66%), gastrointestinal manifestation (47%), orchitis (15%) of boys, and nephritis (24%). One patient with severe nephritis developed pulmonary hemorrhage and acute respiratory distress syndrome. Eleven (14%) patients received corticosteroid therapy. All children made a full recovery, only one patient with nephritis continued to have hypertension at 2 years follow up. Symptoms recurred in 6 (7.7%) patients over a period ranging from one month to 2 years.

Conclusion: Henoch-Schonlein purpura is a mild disease in the eastern province of Saudi Arabia and with no significant differences in the epidemic and clinical profile than that reported elsewhere.

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Henoch-Schonlein purpura (HSP) is an acute inflammatory disorder characterized by a generalized vasculitis of the skin, gastrointestinal (GI) tract, kidney, joints, and rarely testicles, and central nervous system (CNS). It is the most common cause of vasculitis in children worldwide.[1,2] The syndrome takes its name from 2 German physicians. In 1837, John Schonlein first described the purpuric rash and joint pain. Thirty years later, Edward Henoch described the combination of the skin rash and GI manifestation. The reported annual incidence of HSP varies from 6.7-26.7/100,000 children per year.[3,4]

Henoch-Schonlein purpura affects all age groups, but it is most common in children below 10 years, with male preponderance.[5,6] The etiology of HSP remains unknown. However, immunoglobulin A (IgA) clearly plays a crucial role in the immuno-pathogenesis of HSP, as evidenced by increased serum IgA concentration, IgA deposition in the vessel wall, and renal glomeruli.[7,8] The primary process leading to the IgA deposition is believed to result from a defect in IgA1 glycosylation that imbeds IgA1 clearance by the liver.[9,10] Henoch-Schonlein purpura is a self-limited disease; the long term prognosis is directly dependent on the severity of renal involvement.[11,12] Although several reports have dealt with this disease, studies of HSP from Saudi Arabia and the region are scarce.[13-16] In the current report, the author presents the epidemiology and clinical profile of 78 patients with HSP diagnosed at a university hospital in the eastern province of Saudi Arabia over a 15-year period.

Methods. The medical records of all children aged 12 years or less discharged from the Department of Pediatrics, King Fahd Hospital of the University (a tertiary referral center in Al-Khobar area, eastern province of Saudi Arabia) with the diagnosis of HSP from January 1996 to December 2010 were analyzed retrospectively. The study was approved by the Committee for Biological & Medical Ethics (CBME) of University of Dammam.

The inclusion criteria used were the European League Against Rheumatism / Pediatric Rheumatology European Society (EULAR/PReS) endorsed consensus criteria for HSP proposed by Ozen et al[17] as following: Palpable purpura (mandatory criterion) and the presence of at least one of the following 4 features: (1) diffuse abdominal pain, (2) any biopsy showing predominant IgA deposition, (3) arthritis or arthralgia, and (4) renal involvement (any hematuria and/or proteinuria).

The demographic (age and gender) and clinical (trigger factor, seasons of occurrence, appearance of purpura, joint involvement, GI manifestations, renal involvement, other organ involvements) characteristics, laboratory data at onset (white blood cell count, hemoglobin, platelets, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], complement 3 [C3], anti-streptolysin O titer [ASO], throat culture, serum immunoglobulin A, skin and renal biopsy), therapy, and the recurrence in 78 patients were studied. Renal biopsies were graded according to the classification of the International Study of Kidney Disease in Children (ISKDC).[18] Recurrence was defined as a new flare-up of skin rash or other systemic complications following resolution of the disease for at least one month.[5]

Continues variables (such as age) were expressed as mean, median, and range. Absolute numbers as well as percentages were presented for the study variables. As this is a descriptive study, no statistical tests of significance were used.

Results. From January 1996 to December 2010, a total of 78 (46 male and 32 female) children were diagnosed as having HSP. The male to female ratio was 1.4:1. Their ages ranged from 22 months to 12 years, with a mean of 6.3, and median of 6 years. Forty-six percent of patients were less than 5 years of age, and 90% were less than 10 years. Peak incidence of the disease was seen in autumn (26/78; 33.3 %) followed by winter (20/78; 25.6%), summer (19/78; 24.3%), and spring (13/78; 16.6%) **Figure 1**.

Forty-four (56%) of patients had a potential trigger event before HSP onset. Upper respiratory tract infection (URTI) preceded HSP in 41/78 (52.5%) patients. Fever alone in 2/78 (2.5%) and one patient had insect bite. The average time interval between symptoms and the diagnosis of HSP was 9 (2-14) days. The main epidemiological and etiological factors are shown in **Table 1**.

All patients (100%) had non-thrombocytopenic palpable purpura, distributed mainly over the legs, buttocks, and upper extremities. In addition, some had involvement of the face (7 cases). Beside the purpuric rash, one patient with Glanzmann thrombasthenia had ecchymosis on his legs. Skin biopsy in 2 patients displayed leukocytoclastic vasculitis with IgA deposition. Abdominal pain and joint involvement preceded the onset of skin eruption by 1-7 days in 4 (2 each) patients. These patients considered as a typical cases of HSP. Joint involvement (arthralgia and arthritis) occurred in 52/78 (66.7%) patients. The most affected joints were ankles and knees, followed by wrists and hands. One patient suffered from hip pain. Gastrointestinal manifestation was present in 37/78 (47%) patients. Most of them had

abdominal pain. Occult gastrointestinal bleeding was detected in 15/37 (35%) patients. Renal involvement was observed in 19/78 (24%) patients. It manifested by microscopic hematuria in 16/19 (84%) and by gross hematuria in 3 (16%) of patients. Five of the 19 (26%) with hematuria also had proteinuria. Nephritic syndrome developed in 5/19 (26%) patients. A 12-year-old female, with nephritic syndrome, developed pulmonary hemorrhage, and acute respiratory distress syndrome (ARDS) for which she required intubation and mechanical ventilation. Renal biopsy was performed in 3 children with nephritic syndrome, it revealed mesangial proliferation (grade II) in 2 patients and minimal changes (grade I) in one patient. Symptoms and signs of renal involvement resolved over a period ranging from 3 weeks to 2 years. Testicular involvement was present in 7/46 (15%) boys. One patient had testicular exploration and orchioplasty repair for his right testicle. Edema that is confined to feet, hands and face occurred in 8 (10%) children.

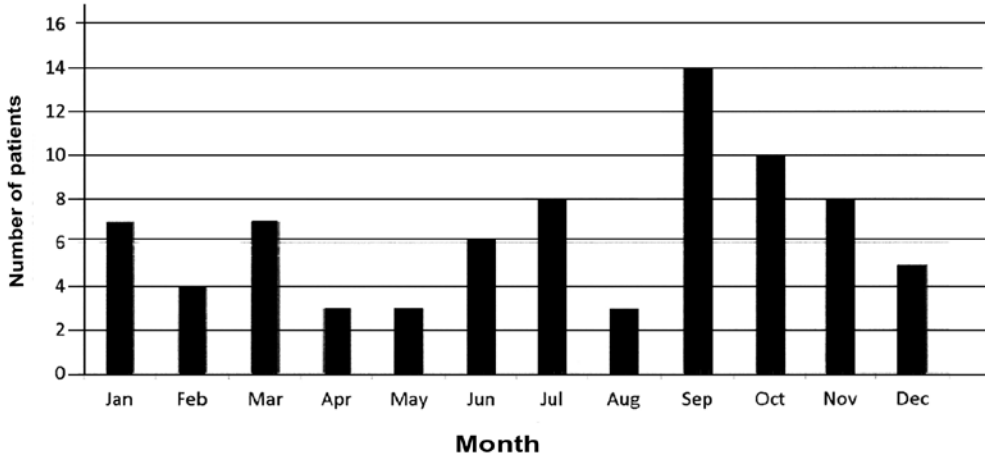

Figure 1 - Seasonal occurrence of Henoch-Schonlein purpura in 78 children.

Table 1 - Demographic data and etiologic factors in 78 children with Henoch-Schonlein purpura.

Demographic data	n (%)
Age at onset (years)	
Range	1.8 - 12
Mean	6.3
Median	6
Gender	
Female	32 (41)
Male	46 (59)
Male to female ratio	1.4:1
Age distribution (years)	
≤5*	36 (46.0)
>5 to ≤10†	34 (43.5)
>10‡	8 (10.0)
Season pattern	
Autumn	26 (33.3)
Winter	20 (25.6)
Spring	13 (16.6)
Summer	19 (24.3)
Etiological factors	44 (56.0)
URTI	41 (52.5)
Fever	2 (2.5)
Insect bite	1 (1.3)
Interval between onsets of symptoms and diagnosis (days)	2 - 14

*male to female ratios: 19:17, †male to female ratio: 24:10, ‡male to female ratio: 3:5, URTI - upper respiratory tract infection

Table 2 - Clinical features of 78 patients with Henoch-Schonlein purpura.

Symptoms	n	(%)
Skin	78	(100)
Joint involvement	52	(66.6)
Arthritis	40	(51.0)
Arthralgia	9	(11.5)
Ankle/feet	37	(47.0)
Knee	18	(23.3)
Wrist/Hand	10	(13.0)
Elbow	2	(2.5)
Hip	1	(1.3)
Gastrointestinal involvement	37	(47.0)
Bowel angina	33	(42.0)
Gastrointestinal bleeding	15	(19.0)
Renal involvement	19	(24.0)
Microscopic hematuria	16	(20.5)
Macroscopic hematuria	3	(3.8)
Protienurea	5	(6.4)
Nephritic syndrome	5	(6.4)
Testicular involvement*	7	(15.0)
Edema of face, dorsa of the feet and hands	8	(10.0)
Seizure	2	(2.5)
Pulmonary hemorrhage	1	(1.3)
Recurrence	6	(7.7)

*boys

Table 3 - Laboratory findings of 78 patients.

Findings	Positive/Tested n	(%)
Anemia (hemoglobin <11 g/dl)	10/78	(12.8)
Leukocytosis (WBC >12 x 10^9/L)	24/78	(30.7)
Thrombocytosis (platelets >500 x 10^9/L)	12/78	(15.3)
Elevated ESR	38/72	(52.7)
Increased C-reactive protein	24/34	(70.5)
Positive ASO titer	11/24	(45.8)
Positive throat culture	0/8	(0)
Low C3	2/31	(6.5)
Elevated IgA (>400mg/dl)	3/28	(10.7)
Renal biopsy	3/78	(3.8)
Skin biopsy	2/78	(2.5)

WBC - white blood cell, ESR - erythrocyte sedimentation rate, C3 - complement 3, ASO - anti-streptolysin O titer

Other clinical features included 2 patients with seizure; one with nephritis and hypertensive encephalopathy, and unprovoked seizure in the other patient. In 6 (7.7%) patients, HSP recurred after complete resolution of symptoms ranging from one month to 2 years. All these 6 patients had non-thrombocytopenic purpura; one had testicular involvement, and one with nephritis. The clinical features of 78 children with HSP are summarized in **Table 2**.

Laboratory finding included leucocytosis in 24/78 (31%) patients. Anemia was detected in 10/78 (13%) and thrombocytosis (platelets >500X10^9/L) in 12/78 (15%) patients. An increased ESR was found in 38/72 (53%) and CRP in 24/34 (70.5%) subjects. **Table 3** summarized the laboratory finding of the patients. No patient had positive throat culture for Streptococcal infection in the 8 specimens tested, but ASO titer was positive in (11/24; 46%) children. Two children had a low level of C3 and serum IgA concentration was elevated in (3/28; 11%). Most of the children received only supportive therapy and simple analgesia. Prednisolone 1-2 mg/kg was prescribed to 11 patients for renal involvement, or joint and GI manifestations. The patient with severe nephritis and pulmonary hemorrhage required high dose pulse methylprednisolone, immunoglobulin, and cyclosporine. All patients made a full recovery; only one patient with nephritis had hypertension at 2 years follow up.

Discussion. Henoch-Schonlein purpura is the most common systemic vasculitis of childhood. In the present study, 78 children (<12 years old) who presented with HSP over a period of 15 years were reviewed. The epidemiological and clinical spectrum of HSP in the eastern province of Saudi Arabia are essentially in agreement with results of other studies from the region and worldwide.[3,13,19] The mean age of the patients in the present study was 6.3 years, and median age 6 years. Nearly 90% of subjects were less than 10 years of age. Of the 78 children, 46 (59%) were boys and 32 (41%) were girls with male to female ratio of 1.4:1. These figures are compatible with several previous reports.[1,15] In children with HSP, males are affected more often than females, with male to female ratio between 1.3:1 and 2:1.[5,20] A slight female preponderance was found in some studies.[21,22] Al-Harbi reported the clinical feature of HSP in the southern part of Saudi Arabia and found nearly equal gender distribution.[14] Henoch-Schonlein purpura occurs throughout the year, but a number of studies have noted seasonal variation, with most patients presenting from fall through spring and a paucity of cases in the summer months.[1,3] In the current study, 59% of patients presented during the fall and winter and 41% presented during the spring and summer months. Nearly 55% of patients had a potential trigger event before HSP onset. Epidemiology clues continue to implicate infectious triggers in HSP.[6,23] Forty-one (56%) patients with current series had an antecedent URTI. Anti-streptolysin O titers were increased in 11 (49%) of the 24 cases in whom it was performed. Several studies reported a positive ASO titer in as much as 50% of patients.[5,24] Farley et al[25] in a case-control study reported a frequency of throat infection in 52% of patients with HSP.

The main clinical features of HSP included purpuric rash, GI symptoms, joint manifestation, kidney, and testicular involvement. Classic skin purpura presented in all patients, in the current study. Rashes were often seen in the lower extremities and buttocks, but some also had involvement of the arms and face. Skin rash persisted from days to weeks. In 8 (10%) of the patients in the current report, the purpura was preceded by arthritis or GI complaints by 2-12 days. The delayed appearance of purpura has been reported in 5-50% of patients.[1,16] Joint involvement is the second most clinical manifestation of HSP. It occurs in 60-80% of cases.[1,2] In agreement with previous literatures, arthritis or arthralgia occurred in 66.7% of the patients in the present study and mainly affecting ankles and knees. The joints of the upper extremities were involved in few patients. One patient had hip involvement a condition rarely reported in the literatures.[6]

Gastrointestinal manifestation has been described in up to 75% of the series.[11,26] Abdominal colic, vomiting, and gross or occult bleeding are the dominant features of GI involvement in 37 (47%) patients, in the current

study. Gastrointestinal symptoms and signs preceded the skin purpura in 6 (8%) patients. No one of the patients developed intussusceptions or perforation. The long term morbidity and mortality of HSP are related to the severity of renal involvement. The reported incidence of renal involvement varies from 10-50%, with end stage renal disease develops in less than 5%.[6,27] In the present series, renal involvement occurred in 19/78 (24%) patients. These figures are consistent with many previous reports, and with the incidence reported by Al-Harbi from southern Saudi Arabia, but it is less than the figures reported by Al-Rasheed et al from Riyadh area, central region of Saudi Arabia.[13,14,28] The low incidence of renal involvement in the current series may be related to local variations in causative and environmental factors. The main clinical features of renal involvement in the present study were microscopic hematuria, with or without protienurea, and nephritic syndrome. Nephritic syndrome developed in 5/19 (26%) patients. One patient with severe nephritis developed pulmonary hemorrhage and ARDS. Pulmonary hemorrhage has a high mortality rate and is usually seen in adolescents and adults.[29,30] Pre-pubertal children are rarely affected, but subclinical lung association is common.[31] A case of HSP complicated with pulmonary hemorrhage and nephrotic syndrome, but treated successfully is reported from Jeddah, Western Saudi Arabia.[32] The overall outcome of HSP nephritis is good. All patients with nephritis in the present study made a complete recovery, but only one patient required treatment for hypertension at 2 years follow up.

Testicular involvement is a well-known complication of HSP. The reported incidence ranged from 3-38% of boys.[33-35] This variability may be partly due to inconsistent inclusion criteria, which ranged from skin edema alone to severe pain. In the current series, 7/46, (15%) males developed scrotal manifestation and in one scrotal exploration were undertaken. HSP with scrotal involvement represents approximately 3% of all cases of acute scrotum.[6] Orchitis may mimic testicular torsion and ultrasound is the gold standard for diagnosis.[36] Seizures are a rare manifestation of CNS involvement in patients with HSP.[1,10] Unprovoked seizure developed in one patient in this series and another patient's seizure complicated hypertensive encephalopathy. There is no diagnostic laboratory test for HSP and most laboratory studies are utilized to exclude other condition that resemble HSP, or to monitor the progress of the disease. In agreement with literature,[6,10,19] the present data show increased ESR in 38/72 (53%), CRP in 24/34 (71%), leucocytosis in 24/78 (31%), anemia in 10/78 (13%), and thrombocytosis in 12/78 (15%) of patients. Increased IgA level was found in 3/28 (11%) patients. Complement component were decreased in 2/31 (6.5%), and none of these children had renal involvement. Decreased complement levels are reported in 10-18% and increased serum IgA in 0-62%.[2,6,16] The frequency of relapses varies from 5-66%.[16,37] In the present study, 6 (7.7%) patients relapsed within the first 2 years. These figures are lower than the reported data from Southern Saudi Arabia, but are similar to the recurrence rate reported by other regional studies.[14,16] Most of the patients with HSP require no management other than supportive measures. Corticosteroid therapy reduces the duration and severity of abdominal and joint pain, but corticosteroids do not prevent the development of nephritis, or alter the natural course of HSP.[10,38] Ten (13%) patients in the present study received steroid for GI and renal involvement. Patients with severe HSP nephritis may require other regimen of treatment. This may include high dose steroid, azathioprine, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin, and plasmapheresis.[39-41] One patient in the current study had severe nephritis and pulmonary hemorrhage successfully treated with immunoglobulin, cyclosporine, and high dose intravenous methylprednisolone.

Study limitation. In this study, we did not include all cases attended the outpatient departments in pediatrics, dermatology, and primary health care clinics. Therefore, this might represents the severe form of clinical presentations.

In summary, HSP is an acute, self-limited disease. Almost all patients in the present report had mild disease and showed full recovery without significant sequelae. The study found no major differences in the epidemic and clinical profile of HSP in eastern Saudi Arabia with that published elsewhere.

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