Henoch-Schönlein's purpura in adults versus children/adolescents: A comparative study

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ABSTRACT

Objectives. *To assess the possible differences in etiological and clinical factors between children/adolescents (< or = 20 years) and adults (> 20 years) with Henoch-Schonlein purpura (HSP).*

Methods. *A retrospective-cum-prospective study of consecutive patients with HSP who presented to our teaching hospital over 5 years. Patients were classified as having HSP according to the criteria proposed by Michel et al and the ACR criteria.*

Results. *102 patients (43 of all patients being male and 59 female) were classified as having HSP; 20 of the patients were adults (mean age 32.1 ± 11.7 years) and 82 were children/adolescents (mean age 6.2 ± 2.6 years). We were unable to identify any precipitating event in 40% of the adults and 37% of the children/adolescents. The frequency of previous drug treatment and of previous upper respiratory tract infection was similar in both groups. At symptom onset, palpable purpura was the chief clinical manifestation in both groups.*

However, renal involvement, in all its aspects, was more frequent and severe in adults. Adults also had a higher frequency of diarrhoea (with or without occult blood) and leucocytosis, but a lower frequency of thrombocytosis.

The frequency of joint manifestations, nausea, vomiting, malena/hematochezia and intussuseption was equal in both groups. Adults required more aggressive therapy, and had a longer hospital stay (10.2 vs. 4.3 days). The outcome was relatively worse in adults, with complete recovery in 18 adults (90%) compared to 81 children/adolescents (98.8%) after a mean ± SD follow up of 2.8 ± 1.7 and 2.4 ± 1.3 years, respectively.

Conclusions. *In adulthood, HSP is a more severe clinical syndrome, with a higher frequency of diarrhoea and renal involvement. Adults also require aggressive treatment more frequently and have a longer hospital stay.*

Introduction

Henoch-Schönlein's purpura (HSP) is an immune-complex mediated vasculitis affecting small vessels in skin, gut and glomeruli (1). In its fully expressed form it is characterised by palpable purpura, arthritis, bowel involvement, and glomerulonephritis. Histopathologically it is characterized by polymorphonuclear leukocytic infiltration of the vessel wall with leukocytoclasia, and immunofluorescence reveals IgA deposits (2, 3).

Though HSP is primarily a disease of childhood and adolescence, several reports have described the disease in adults (4-8). There are 3 previous studies that have compared and contrasted the disease spectrum as seen in adults with that seen in children/adolescents (9-11). These studies have originated from Spain, Israel, and China respectively. An Italian study has compared the progression of renal disease in children and adults with Henoch-Schönlein purpura (HSP) nephritis (12). To date there are no such studies from the Middle East. Since HSP is a fairly common clinical condition among children/adolescents and adults in Kuwait (13, 14) we undertook the present study to compare the various clinical and laboratory characteristics of HSP in adults versus children/adolescents.

Materials and methods

Background

Adult and paediatric rheumatology services are available at Mubarak Al Kabeer and Amiri Hospitals. Depending on the designated residential areas, polyclinics (approximately 70) and 5 other general hospitals refer their rheumatology patients to these two hospitals. The present study is on patients from Mubarak Al Kabeer Hos-

pital, which is the teaching hospital for Kuwait University, Faculty of Medicine.

Study design

This is a retrospective-cum-prospective study of 102 patients covering a period of 5 years, from mid-1998 to mid-2003. It included 76 patients who were already under follow up in our clinics, with the others being recruited prospectively. Patients satisfying 3 or more of the following 6 criteria for HSP proposed by Michel *et al.* (15) were identified: a) palpable purpura; b) abdominal angina; c) gastrointestinal bleeding; d) hematuria; e) age < 20 years; and f) absence of responsible medication. Adult patients were also required to fulfil three of these criteria to the exclusion of 'age at onset < 20' criteria. Patients satisfying fewer than three criteria were said to have hypersensitivity vasculitis and were excluded from the study (15). These criteria were chosen as they do not require histological confirmation of the diagnosis. However, all patients also satisfied 2 of the following 4 ACR criteria for HSP (16): a) palpable purpura (non-thrombocytopenic); b) age ≤ 20 at disease onset; c) bowel angina: diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea; d) histologic changes showing granulocytes in the walls of arterioles or venules.

Patients older than 20 were considered adults, and those 20 years of age or younger were considered children/adolescents. This cut-off age of 20 was chosen for two reasons: this age was proposed as a criterion for HSP by the ACR (age < 20 at symptom onset) (16), and because this age best discriminated HSP from hypersensitivity vasculitis in the study by Michel *et al.* (15). The patients were evaluated clinically and appropriately investigated. All clinical data including demographic pattern, ethnic trend, seasonal occurrence, possible etiological factors, clinical manifestations and relevant laboratory parameters was entered for both groups of patients into a predesigned proforma. Those with cutaneous vasculitis secondary to collagen vascular disease, neoplasia, severe infection, and those with other well defined clinical entities were excluded. All patients who were RF, ANA, or ANCA positive were excluded. Skin biopsy was done in all adults to confirm the presence of leucocytoclstic vasculitis and vascular deposition of IgA immune complexes. In children/adolescents it was done in selected cases only. All procedures followed were in accordance with the Helsinki Declaration of 1975/83.

Clinical definitions (17)

Severe disease

Patients with GI complications (bleeding, obstruction, or intussusception), neurological involvement, myocarditis, alveolar hemmorhage and severe nephropathy (see below) were considered to have severe disease.

Renal involvement

Renal involvement was categorized as mild or severe. Mild nephropathy was present if the patient had hematuria and/or proteinuria that was not in the nephrotic range, with normal renal functions. Severe nephropathy was present if the patient had nephrotic syndrome (i.e., plasma albumin of less than or equal to 25gm/liter and either 1 gm of proteinuria/day/m^2 of body surface area or more than 3.5gm of proteinuria/day) (18) with or without edema and/or acute nephritic syndrome (i.e., hematuria with at least 2 of the following: hypertension, increased plasma urea or creatinine, and oliguria). Renal insufficiency was considered to be present if the plasma creatinine concentration was > 125% of the upper limit of normal and or the estimated glomerular filtration rate (EGFR) was < 60 ml/min (18).

Aggressive drug treatment

Patients requiring steroids and/or immunosuppressive treatment with azathioprine or cyclophosphamide were categorized as having received aggressive drug treatment.

Corticosteroids were prescribed because of persistent skin lesions or because of visceral involvement, such as severe abdominal pain, gastrointestinal bleeding, or severe nephropathy. Cytotoxic drugs were prescribed either as steroid sparing agents or as additional therapy for severe renal or other systemic involvement.

Indications of longer hospital stay

Patients requiring extensive workup or having severe disease and requiring aggressive drug treatment were hospitalized for longer periods till stabilization of their clinical status.

Analysis

The two groups, viz. adult and the pediatric age groups, were compared with the Z-test for two proportions and a probability level of < 0.05 was considered statistically significant. The Z-test evaluates the difference between two proportions from two independent samples, and is defined by Z = (p1-p2)/SE (p1-p2), where p1 and p2 respectively are two proportions from two independent samples and SE is the standard error of the difference (p1-p2).

Results

The results of the comparison between children/adolescents and adults are given in Tables I and II. The preceding and demographic factors are given in Table I and clinical features are given in Table II.

General and demographic features

During the period of 5 years a total of 102 patients with HSP were seen, of which 20 were adults (mean age 32.1 ± 11.7 years) and 82 were children/adolescents (mean age 6.2 ± 2.6 years). There was no significant difference in the percentage of females (70 vs. 55) among adults and children/adolescents respectively.

Seasonal pattern

The majority of both adult (60%) and juvenile (67%) patients presented during fall and winter months (September-February) as against spring and summer months. However, these differences were not statistically significant.

Preceding factors

Antecedent respiratory infections and prior antibiotic exposure were common etiological factors in both groups and the inter-group differences were not significant. History of recent immu-

Table I. Comparison of demographic, ethnic, and seasonal characteristics of HSP in adults and children.

Serial Number	Parameter	Adults (n = 20)		Children/ Adolescents (n = 82)		P value
		N	%	N	%	
1.	Females	14	70.0	45	54.9	0.2230
2.	Presentation in fall/winter	12	60.0	55	67.1	0.5546
3.	Etiological factors					
	• Unknown	8	40.0	30	36.6	0.7780
	• Upper respiratory infection	10	50.0	37	45.1	0.6874
	• Drugs (mostly antibiotics)	2	10.0	6	7.3	0.6870
	• Immunization	0	0.0	8	9.8	0.1446
	• Insect bite	0	0.0	1	1.2	0.6226

Note: none of the values are statistically significant.

Table II. Comparison of clinical and laboratory characteristics of HSP in adults and children.

Serial Number	Parameter	Adults (n = 20)		Children/ Adolescents (n = 82)		P value
		N	%	N	%	
1.	Purpura	20	100	82	100	1.0000
2.	Gastrointestinal involvement	11	55.0	50	60.9	0.6836
	• Abdominal pain	8	40.0	42	51.2	0.3690
	• Nausea, vomiting	4	20.0	16	19.5	0.9598
	• Diarrhea	5	25.0	4	4.9	**0.0045**
	• Malena / haematochezia	3	15.0	9	11.0	0.6188
	• Intussuception	1	5.0	3	3.7	0.3856
	• Obstruction	0	0	0	0	-
3.	Joint symptoms (arthritis/arthralgia)	11	55.0	58	70.7	0.1784
4.	Nephropathy	18	90.0	43	52.4	**0.0190**
	• Haematuria	17	85.0	40	48.8	**0.0035**
	• Non-nephrotic proteinuria	6	30.0	17	20.7	0.3720
	• Mild nephropathy	15	75.0	42	51.2	**0.0546**
	• Severe nephropathy	3	15.0	1	1.2	**0.0428**
	• Renal failure	2	10.0	1	1.2	**0.0362**
5.	Leukocytosis (>10.5 $X10^9$/l	12	60.0	12	14.6	**< 0.001**
6.	Increased platelets (400 $X10^9$/l)	0	0.0	16	19.5	**0.0316**
7.	Aggressive drug treatment required	9	45.0	7	8.5	**< 0.001**
8.	Hospital stay in days (± SD)	10.2 (9.2)		4.3 (3.3)		**< 0.001**

Note: p values in bold are statistically significant.

nization was an important factor in children/adolescents.

Clinical features and investigations

Purpura was universally present in both groups. As far as gastrointestinal manifestations are concerned, abdominal pain, nausea, vomiting, and malena/-hematochezia were seen with nearly equal frequency in both groups, whereas diarrhoea occurred with greater frequency in adults. Two of the 5 adults and one of the 4 children with diarrhea had occult blood positive in the stools. One adult aged 28 years had intussuception, compared to 3 children.

Joint manifestations were more frequent in children/adolescents, but not significantly so.

Among renal manifestations, the frequency of overall renal involvement, as also the frequency of mild nephropathy, severe nephropathy, and renal failure was significantly more in adults compared to children/adolescents. Notably, the frequency of haematuria in adults was nearly twice that seen in children/adolescents. Fifteen adults had mild nephropathy, and 3 had severe nephropathy, of which one had nephrotic syndrome, and two had uraemia. All 17 adult patients with hematuria continued to have this abnormality during the follow up period. Of the 6 patients with non-nephrotic range proteinuria, two remitted, whereas the remaining 4 had persistence of this abnormality. On kidney biopsy, done on 3 adult patients, 1 had focal glumerulosclerosis and 2 had severe necrotizing glomerulonephritis. All three biopsies showed IgA deposition on immunoflourescence. The patient with nephrotic syndrome developed chronic renal failure, whereas, of the two patients with severe necrotizing glomerulonephritis, one patient had persistent stable renal failure while the other went into end stage renal disease requiring dialysis and subsequent transplantation. There were no deaths. In contrast, both the renal involvement and outcome were remarkably benign in children/adolescents. Mild nephropathy was present in 51% of them. Only one had severe renal involvement progressing to end stage renal failure. All other children/adolescents recovered uneventfully.

Leukocytosis was prominent among adults, whereas increased platelets were observed only in children/adolescents. One adult patient had ECG and echo evidence of myocarditis

Treatment, hospital stay and follow-up

Aggressive treatment was required in 9 adults, comprising 3 with severe nephropathy, 3 with severe abdominal pain and/or gastrointestinal bleeding, and 3 with persistent skin lesions and/or refractory arthritis. On the other hand, 7 children/adolescents required aggressive therapy, 6 for severe gas-

trointestinal involvement and 1 for nephritis, with good results. Aggressive therapy consisted of steroids and/or immunosuppressive treatment with azathioprine or cyclophosphamide.

The mean duration of hospital stay was significantly higher for adults as compared to children/adolescents ($p < 0.001$). The period of follow up was 2.8 ± 1.7 years and 2.4 ± 1.3 years among adults and children respectively.

Discussion

General and demographic features

HSP is an immune-complex mediated small vessel vasculitis with IgA dominant immune-deposits (1) that occurs mainly in children/adolescents (19). However, adult onset HSP is not uncommon, with the ratio of childhood/adolescent vs. adult onset HSP being 2-3:1 in reported series (10, 11, 17) and being 4:1 in our series. Hence it merits more attention. Slight male preponderance has been reported both in adults (17) and children/adolescents with HSP (11). In contrast, we find that females outnumber males in both groups in our study, though the differences are not significant.

Seasonal pattern

There does not seem to be any consensus on seasonal variation in HSP, with different groups reporting different findings (3, 9, 10, 17), The majority of our patients in both groups tended to present in winter/fall. Interestingly, the seasonal distribution of asthmatic attacks in Kuwait also shows maximum rates during the winter (20) and the main season for attacks of allergic rhinitis in this country are the fall months of September-October (21). One is tempted to contemplate weather similar seasonal antigens are involved in the etiopathogenesis of these three seemingly diverse allergic entities.

Preceding factors

The frequency of previous drug treatment, primarily antibiotics or analgesics, is known to be similar in both children/adolescents and adults (19), and our study confirms this. On the other hand, it does not show that previous upper respiratory tract infection is more frequent among the children/adolescents, as previously reported (19). No precipitating event was found in 72% of the adults and 66% of the children/adolescents in one series (17), whereas in our study the figures were 40% and 37% respectively. A recent study found that though a history of upper respiratory tract infection seems to be associated with a higher incidence of nephritis in children with HSP, it does not influence the outcome of the disease (22).

Gastrointestinal involvement

GI symptoms occur in 40% to 60% of patients with HSP. These include colicky pain, nausea, vomiting, upper GI bleeding, diarrhoea, and bloody stool and are potentially the most serious manifestations (19). 55% and 61% of the adults and children/adolescents in the present series had gastrointestinal involvement. Of the various manifestations, abdominal pain was noted to be less frequent in adults in our series (40 vs 51%) as in some earlier reported ones(11, 17). In contrast we found a higher frequency of diarrhoea in adults, a finding not reported earlier. Nausea, vomiting and gastrointestinal bleeding were equally frequent in both groups.

Joint involvement

The frequency of joint involvement is known to be similar in adults and children/adolescents (10, 11, 17), we also found this to be the case.

Renal involvement

Though nephritis may occur in up to 50% of children/adolescents with HSP, the renal disease is usually milder in them and almost always heals (19). This was found to be true in our series also, with all but 1 (1.2%) of the 43 children/adolescents with renal involvement recovering completely. In adults, on the other hand, several studies have documented not only greater frequency and severity of renal involvement but also high long term risk of renal dysfunction (6, 8, 9, 11, 17, 23, 24). Some other studies, however have found an equal frequency, similar severity, and favourable outcome in both groups (7, 10). The findings of our study indicate a greater frequency and severity of renal disease in adults. Thus, haematuria was seen to be nearly twice as common in adults as in children/adolescents. Nephropathy occurred in 95% of adults compared to only 52% of children/adolescents. Severe nephropathy was seen in 3 (15%) of 20 adults, two of whom progressed to renal failure.

Laboratory investigations

Though white cell and platelet counts are characteristically normal in HSP (19), leucocytosis and thrombocytosis can occur as an acute phase response. We found a higher frequency of leucocytosis and lower frequency of thrombocytosis in adults compared to children/adolescents. Secondary thrombocytosis is often more pronounced in childhood in association with any inflammatory syndrome.

Disease severity, treatment, and hospital stay

Our study confirms the observation of some previous series that adults have more frequent and severe disease, particularly renal involvement (9, 11, 17, 24). Consequently adults require more aggressive therapy, consisting of steroids and/or cytotoxic agents, as seen in our study. The period of hospital stay was observed to be significantly longer in adults. This could be explained not only by the requirement of more extensive workup (including skin biopsy) required for excluding underlying connective tissue disease, necrotising vasculitis or malignancy, but also by the requirement of more aggressive treatment in them.

In conclusion, the clinical picture of HSP in adults is similar to that in children, though the frequency and severity of renal involvement is greater in them. Adults also require more aggressive treatment and have a longer hospital stay.

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