Henoch-Schönlein purpura in children from western Turkey: a retrospective analysis of 430 cases

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SUMMARY: Anıl M, Aksu N, Kara OD, Bal A, Anıl AB, Yavaşcan Ö, Ün B. Henoch- Schönlein purpura in children from western Turkey: a retrospective analysis of 430 cases. Turk J Pediatr 2009; 51: 429-436.

The medical records of children discharged with a diagnosis of Henoch-Schönlein purpura (HSP) between January 1996 and March 2006 were analyzed retrospectively. The patient population consisted of 430 children (225 boys, mean age: 7.9±2.9 years; range: 2-14 years). At onset, purpura was present in all cases, arthritis/arthralgias in 195 (45.3%), abdominal involvement in 148 (34.4%), and renal involvement in 192 (44.7%). Purpura manifested after 24 hours of admittance in 64 patients (14.9%) (atypical cases). Multivariate analysis showed that female sex, atypical presentation and early corticosteroid treatment increased the risk of renal involvement ($p<0.05$). Recurrences, occurring in 22 (5.2%) patients, were correlated with early corticosteroid treatment ($p<0.05$). After a mean 17.3±2.9 months of follow-up, no patient had renal insufficiency. Female sex, atypical presentation and early corticosteroid treatment were considered to increase the risk of developing renal involvement, and relapses occurred more frequently in children treated with corticosteroid. Our study confirmed that HSP is generally a benign disease in children from western Turkey.

Key words: Henoch-Schönlein purpura, female sex, atypical cases, corticosteroid treatment, renal involvement, recurrence.

Henoch-Schönlein purpura (HSP) is an acute small-vessel leukocytoclastic vasculitis. HSP is the most common vasculitis in children, with an incidence of about 10 cases per 100,000 annually[1]. It is characterized by cutaneous, articular, gastrointestinal (GI) and renal involvement, while orchitis, vasculitis of the central nervous system (CNS) and pulmonary hemorrhage are rare findings[2]. Renal involvement is the principal prognostic determinant in HSP[1,3].

Henoch-Schönlein purpura shows a wide but variable geographic distribution. Despite the rather high incidence of HSP, its clinical characteristics and prognosis have been poorly documented. Moreover, reported studies enrolling a large number of HSP patients are rare. In this study, we retrospectively evaluated the epidemiological and clinical data, main laboratory abnormalities, therapy, and outcome in 430 patients with HSP followed by a single center, over a follow-up period of at least one year. Moreover, we searched for the predictors of renal involvement and relapse, analyzing all of the above-mentioned findings.

Material and Methods

The medical records of all children discharged from the Department of Pediatrics at the Tepecik Training and Research Hospital (a tertiary referral center in İzmir, in the western part of Turkey) with a diagnosis of HSP from January 1996 to March 2006 were analyzed retrospectively. Diagnosis was made based on the American College of Rheumatology criteria[4]. Patients were diagnosed as HSP if they met at least two of the criteria:[1] palpable purpura, not related to thrombocytopenia,[2] age <20 years at the disease onset,[3] bowel angina, and[4] histologic changes showing granulocytes in the walls of arterioles and venules. A minimum follow-up period of one year was one of the inclusion criteria.

An atypical HSP case was defined as a HSP patient without skin rash in the first 24 hours of admittance.

The demographic (age and sex) and clinical (trigger factor, seasons of occurrence, presence of purpura, joint involvement, GI manifestations, renal involvement, other organ involvements) characteristics, laboratory data at onset (white blood cell count, hemoglobin, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], complement 3, serum immunoglobulin A), therapy, and the recurrence (relapse) in 430 patients were studied.

Hypertension was defined as an average systolic or diastolic blood pressure ≥95th percentile for age, sex and height.

Ranges for normal laboratory data defined in Nelson's Textbook of Pediatrics were used as reference values[5]. HSP nephritis (HSN) was defined as the presence of gross or microscopic hematuria with or without proteinuria. Hematuria was defined as small amount (+) of hemoglobin on dipstick testing or >5 red blood cells per high power microscopic field in a centrifuged specimen. Proteinuria was defined as small amount of protein (+) on dipstick testing or proteinuria >4 mg/m^2/hour obtained from 24-hour collected urine.

Low creatinine clearance was defined as an estimated glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2 body surface area, using Schwartz formula.

Henoch-Schönlein nephritis patients were classified into five grades according to the initial clinical presentation. The modified Meadow classification[3,6] used is as follows: Grade 1, microscopic hematuria; Grade 2, persistent mild proteinuria (<20 mg/m^2/h) and/or hematuria; Grade 3, nephritic syndrome (hematuria, low GFR, oliguria, hypertension, edema); Grade 4, nephrotic syndrome (proteinuria >40 mg/m^2/h, hypoalbuminemia, hyperlipidemia, edema); and Grade 5, mixed nephritic-nephrotic syndrome. Indications for renal biopsy were persistent proteinuria, persistent hematuria, nephrotic or nephritic syndrome, or hematuria with renal failure. Renal biopsies were performed during the first month after the appearance of the initial findings of HSN. Renal biopsies were graded from I to V in increasing severity according to the classification of the International Study of Kidney Disease in Children (ISKDC), as follows:[1] Grade I, minimal glomerular abnormalities;[2] Grade II, pure mesangial proliferation, focal or diffuse;[3] Grade III, crescents/segmental lesions <50%, focal or diffuse;[4] Grade IV, crescents/segmental lesions 50-75%, focal or diffuse;[5] Grade V, crescents/segmental lesions >75%, focal or diffuse; and Grade VI, pseudo mesangiocapillary changes.

Clinical outcome was graded according to Meadow's criteria[6]: A, normal (no hypertension, no urinary abnormality and normal plasma creatinine concentration); B, minor urinary abnormalities (proteinuria <20 mg/m^2/h with or without microscopic-recurrent macroscopic hematuria); C, active renal disease (proteinuria >20 mg/m^2/h and/or elevated plasma creatinine level); and D, renal insufficiency (GFR <60 ml/min/1.73 m^2).

A relapse was defined as a new flare-up of skin lesions or other systemic complications following resolution of the disease for at least two weeks[7].

In our department, we routinely prescribe benzathine penicillin (<27 kg: 600,000 units; ≥27 kg: 1,200,000 units, single dose, intramuscular [im]) within the first 24 hours of admittance. In the exception of renal involvement, oral systemic corticosteroids (prednisolone 1 to 2 mg/kg/day for 7 days followed by a gradual reduction in dosage over 2 to 3 weeks) were indicated for treatment of severe GI involvement (severe abdominal pain and/or gross intestinal bleeding)[2].

Statistical Package for the Social Sciences (SPSS version 13.0 for Windows) was used for statistical analysis. Continuous data were described as means and standard deviations (mean±SD). Categorical variables were expressed as percentages. Continuous variables were analyzed by Student-*t* test or Mann-Whitney U test. Categorical variables were analyzed by chi-square (Pearson). Relative risks were calculated. The stepwise logistic regression analysis was used for multivariate analysis. A *P* value of less than 0.05 was considered to be significant.

Results

Between January 1996 and March 2006, 430 children fulfilling the inclusion criteria described above in the "Methods" section were selected. Males and females were affected nearly equally

(male/female ratio: 1.09). One hundred sixty-four patients (38.1%) had a potential trigger event before HSP onset. Upper respiratory tract (URT) infection preceded HSP in 139 (32.3%). The previous infective conditions other than URT, lower respiratory tract (LRT) and GI infections were scarlet fever in 3, chicken pox in 3, lymphadenitis in 2, impetigo in 2, and mumps in 1. One child had been given an influenza vaccination 10 days before the onset of HSP. The main epidemiological and etiological factors are shown in Table I.

The clinical manifestations of 430 children with HSP are summarized in Table II. All patients had non-thrombocytopenic palpable purpura. The skin lesions were distributed over the buttocks and legs in 338 (78.6%) cases. Besides the typical purpuric rash, other skin lesions (nodular, macular, papular, urticarial or vesicular) were observed in 32 (7.4%) patients. In 366 (85.1%) cases, the skin lesions were the presenting symptoms of HSP. Sixty-four (4.9%) children exhibited skin lesions after 24 hours of admittance, defined as atypical cases, in which GI and joint involvements were apparent before the skin lesions in 42 and 22 cases, respectively. Of the study group, 85 patients showed isolated palpable purpura. A skin biopsy was performed in 27 of these children, and displayed IgA deposits in only

Table I. Demographic Data and Etiologic Factors in 430 Children with Henoch-Schönlein Purpura

Age at onset (year)	
Mean±SD	7.9±2.9
Range	2-14
Median	8
Sex	
Female, n (%)	205 (47.7)
Male, n (%)	225 (52.3)
Male/female ratio	1.09
Follow-up (month)	
Mean±SD	17.3±2.9
Range	13-46
Median	19
Seasonal pattern, n (%)	
Autumn	155 (36)
Winter	120 (28)
Spring	99 (23)
Summer	56 (13)
Possible etiological factors, n (%)	
Unknown	266 (61.9)
URT infection	139 (32.3)
LRT infection	5 (1.2)
GI infection	3 (0.7)
Vaccination	1 (0.2)
Insect bite	5 (1.2)
Other infection	11 (2.6)

SD: Standard deviation. URT: Upper respiratory tract. LRT: Lower respiratory tract. GI: Gastrointestinal.

Table II. Clinical Features in 430 Patients with Henoch-Schönlein Purpura

Symptom	n	%
Skin rash	430	100
Joint manifestations	195	45.3
Arthritis	156	36.3
Arthralgia	39	9.1
Gastrointestinal manifestations	148	34.4
Bowel angina	130	87.8
Vomiting/nausea	22	14.9
Positive fecal occult blood	80	54.0
Melena	8	5.4
Hematemesis	2	1.3
Intussusception	4	2.7
Renal involvement	192	44.7
Hypertension	35	8.1
Scalp edema	2	0.5
Subcutaneous edema in dorsa of the hands and feet	26	6.0
Subcutaneous edema of the scrotum (n/♂)	6/199	3.0
Nervous system involvement	3	0.7
Atypical presentation*	64	14.9

*No skin rash within 24 hours.

19. Joint involvement occurred in 195 of 430 children (45.3%). The most frequently affected joints were ankles (122 cases) and knees (53 cases). Involvement of wrists (8 cases), hands (7 cases) and elbows (5 cases) was less common. There were GI manifestations in 148 (34.4%) patients. Ninety children (20.9%) experienced GI bleeding. CNS involvement occurred in 3 patients, and the neurological symptoms were headache (2 patients) and seizure (1 patient). Nearly half of the children (192 children, 44.7%) had urinary abnormalities of varying degree. The majority of the HSN patients had only microscopic hematuria (26.3%) (Table III). Renal biopsy was performed in 12 children and revealed Grade I in 2 (16.7%), Grade II in 4 (33.3%) and Grade III in 6 (50%) patients.

Table III. Renal Involvement According to the Modified Meadow Classification in 192 HSN Children

Modified meadow classification	n	%
Grade 1	113	26.3
Grade 2	55	12.8
Grade 3	9	2.1
Grade 4	6	1.4
Grade 5	9	2.1

HSN: Henoch-Schönlein purpura nephritis.

The clinical outcome of 192 HSN children was graded according to Meadow's criteria. One hundred eighty-seven children (97.4%) were in Grade A, 4 (2.1%) in Grade B and 1 (0.5%) in Grade C.

An increased ESR was detected in 173 of 190 (91%) patients, increased CRP in 120 of 159 (75.4%), and leukocytosis in 107 (24.9%). No patient showed decreased serum complement 3 (0/151 patients) or increased serum IgA levels (0/126 patients).

All patients received benzathine penicillin. One hundred fifty-two (35.3%) and 42 (9.7%) children were given paracetamol and nonsteroidal anti-inflammatory drugs, respectively. A total of 104 patients (24.2%) received corticosteroids during the first month of HSP, due to severe GI involvement in 102 and severe nephropathy in 2 cases. These patients were treated with oral prednisolone (1-2 mg/kg per day). The duration of corticosteroid therapy ranged from 7 to 47 days (mean: 12.3±3.2 days).

Among 430 patients with HSP, 24 recurrences occurred in 22 (5.2%) patients over a period of time ranging from 2 to 12 months. Most of the children (19 cases, 86.3%) had only one relapse. One patient showed two relapses. Three relapses occurred in one patient.

There were statistically significant differences between patients with and without nephritis in sex (p=0.03, odds ratio [OR]=1.23, 95% confidence interval [CI]=1.022-1.487), GI bleeding (p=0.03, OR=1.646, 95%CI=1.032-2.627), atypical presentation (p=0.00, OR=2.749, 95%CI= 1.576-4.795), and steroid treatment (p=0.00, OR=2.226, 95%CI=1.419-3.491) (Table IV). When analyzed by a multivariate logistic regression analysis, sex, atypical presentation and steroid treatment were found to have prognostic value (p<0.05) (Table V).

Univariate analyses of the risk factors relating to HSP recurrence showed significant correlation with steroid treatment (p=0.01, OR= 2.784, 95%CI=1.166-6.646) (Table VI). By multivariate analysis, steroid treatment was again found to be a risk factor for relapse (p=0.021, OR=2.784, 95%CI=1.166-6.646).

Discussion

To our knowledge, this study provides one of the largest patient series on HSP in children. In the present study, 430 children who presented with HSP over a period of 10 years were analyzed. Since this study included children who were diagnosed by HSP during the period between January 1996 and March 2006, the diagnosis of all children with HSP was made according to the American College of Rheumatology criteria[4]. Therefore, the classification criteria used in this paper were the American College of Rheumatology criteria. However, very recently, a new and more realistic criteria, EULAR/PreS endorsed consensus criteria (2006), has been proposed[8]. According to this new classification, aside from palpable purpura, which is a mandatory criterion, one of the following must co-exist: 1) diffuse abdominal pain; 2) any biopsy showing predominant IgA deposition; 3) arthritis or arthralgia; and 4) any renal involvement. This classification also deleted the age criterion. In our study, 85 children showed isolated palpable purpura (without other features). Of these 85 children, 27 patients underwent skin biopsy, of whom

Table IV. Univariate Analysis of Prognostic Factors in 430 Patients Associated with Renal Involvement

	HSP nephritis (–) n=238, mean±SD/n (%)	HSP nephritis (+) n=192, mean±SD/n (%)	P	OR	95% CI
Age (year)	7.5±2.8	7.9±2.8	017	–	–
Sex (♀)	102 (42.8)	103 (53.6)	0.03	1.23	1.022-1.487
Purpura	238 (100)	192 (100)	0.99	–	–
Joint involvement	111 (46.6)	84 (43.7)	0.55	–	–
GI involvement	75 (31.5)	73 (38)	0.15	–	–
GI bleeding*	41 (17.2)	49 (25.5)	0.03	1.646	1.032-2.627
Melena	7 (2.9)	3 (1.5)	0.34	–	–
Intussusception	3 (1.2)	1 (0.5)	0.42	–	–
Subcutaneous edema in dorsa of the hands and feet	11 (4.6)	15 (7.8)	0.16	–	–
Scalp edema	0	2 (1)	0.11	–	–
Hypertension	17 (7.1)	18 (9.3)	0.40	–	–
Nervous system involvement	1 (0.4)	2 (1)	0.44	–	–
Atypical presentation	22 (9.2)	42 (21.8)	0.00	2.749	1.576-4.795
Steroid treatment	42 (17.6)	62 (32.2)	0.00	2.226	1.419-3.491
Leukocytosis	50 (21)	57 (29.6)	0.08	–	–
Anemia	52 (21.8)	49 (25.5)	0.37	–	–
Elevated CRP	62 (26)	57 (29.6)	0.27	–	–
Elevated ESR	97 (40.7)	76 (39.5)	0.49	–	–
Relapse	8 (3.3)	14 (7.2)	0.06	–	–

*: Positive fecal occult blood test plus melena plus hematemesis.
OR: Odds ratio. CI: Confidence interval. GI: Gastrointestinal. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate.

Table V. Multivariate Analysis by Logistic Regression of Prognostic Factors in 430 Patients Associated with Renal Involvement in Henoch-Schönlein Purpura

Variable	P	OR	95% CI
Sex	0.007	1.726	1.161-2.566
Atypical presentation	0.005	2.300	1.278-4.139
Corticosteroid treatment	0.006	1.960	1.213-3.167

OR: Odds ratio. CI: Confidence interval.

Table VI. Univariate Analysis of Prognostic Factors in 430 Patients Associated with Recurrence

	Relapse (–) n=408 mean±SD or n (%)	Relapse (+) n=22 mean±SD or n (%)	P	OR	95% CI
Age (year)	7.7±2.8	8.1±2.1	0.42	–	–
Sex (♀)	195 (47.7)	10 (45.4)	0.83	–	–
Purpura	402 (98.5)	21 (95.4)	0.26	–	–
Joint involvement	186 (45.5)	9 (40.9)	0.66	–	–
GI involvement	140 (34.3)	8 (36.3)	0.84	–	–
GI bleeding*	86 (21)	4 (18.1)	0.74	–	–
Melena	10 (2.4)	0	0.45	–	–
Intussusception	3 (0.7)	1 (4.5)	0.07	–	–
Renal involvement	178 (43.6)	14 (63.6)	0.06		
Subcutaneous edema in dorsa of the hands and feet	24 (5.8)	2 (9)	0.53	–	–
Scalp edema	2 (0.4)	0	0.74	–	–
Hypertension	33 (8)	2 (9)	0.86	–	–
Nervous system involvement	3 (0.7)	0	0.68	–	–
Atypical presentation	60 (14.7)	4 (18.1)	0.65	–	–
Corticosteroid treatment	94 (23)	10 (45.4)	0.01	2.784	1.166–6.646
Leukocytosis	102 (25)	5 (22.7)	0.94	–	–
Anemia	94 (23)	7 (31.8)	0.34	–	–
Elevated CRP	113 (27.6)	6 (27.2)	0.80	–	–
Elevated ESR	163 (39.9)	10 (45.4)	0.30	–	–

*: Positive fecal occult blood test plus melena plus hematemesis.
OR: Odds ratio. CI: Confidence interval. CRP: C-reactive protein. ESR: Erythrocyte sedimentation rate.

19 showed IgA deposition. Considering the recent EULAR/PreS endorsed criteria for the classification of childhood vasculitides, HSP should have been diagnosed in only 364 of 430 children. However, in our series, based on EULAR/PreS criteria, it is not clearly stated whether the remaining 58 patients who did not undergo a skin biopsy had HSP.

Henoch-Schönlein purpura occurs most frequently between the ages of 5 and 15 years, with a mean age of about 4 to 7 years[2,7,9]. In the present study, the median age of our patients was 8 years. Male predominance was found in some studies[7,9-11]. By contrast, in the Garcia-Porrua[12] and Calvino[13] studies, HSP in children was more common in females. In our cohort, the male/female ratio was nearly equal.

As previously reported[7,9-11], in the present series, most of the children developed HSP in the autumn, winter, and spring, with the lowest incidence in the summer. Although its cause is still unknown, HSP is often associated with infectious agents[1,7,9]. Analysis of our results showed that nearly 40% of the patients experienced a potential trigger event before HSP onset, and in up to 80% of them, an upper respiratory infection preceded the disease.

Cutaneous purpura is the essential element in the diagnosis of HSP[1]. According to the literature, GI symptoms are the presenting features in about 12-20% of patients, and joint symptoms in about 15-25%[7,10]. In our cohort, the abdominal and joint involvements preceded the cutaneous lesions in 10% and 5% of the cases, respectively. We named these patients as atypical cases for investigating the clinical predictor value in renal involvement and recurrence. In agreement with the literature[1,7,13], joint involvement was the second most common feature of HSP, occurring in roughly 45% of patients and most often affecting the knees and ankles. GI involvement occurs in 50-75% of patients. Colicky abdominal pain, vomiting, and GI bleeding are the dominant features[1,7,10,13]. In the present study, GI involvement occurred in 34% of patients, GI bleeding in 20%, and vomiting-nausea in 5%. As in our series, intussusception is uncommon[7,10,13]. Localized edema was present in 8% of patients, mostly localized at the ankles and feet. More rarely, the scalp was involved. Testicular involvement was noted in 3% of patients. These findings are lower than in the literature[7,10,11]. Nervous and pulmonary involvements in HSP are rare[1,7]. In our report, only three children complained of nervous system involvement and no cases had pulmonary involvement.

The clinical course of HSP in children is variable, with some patients having a much more rapidly progressing course than others. The long-term morbidity and mortality of HSP is related mainly to the severity of renal involvement. The incidence of renal involvement varies from 10-60%[1-3]. In the present study, renal involvement occurred in 45% of the whole group. Most of our patients with renal involvement developed mild urinary abnormalities, which is similar to the literature[3,7,9,13]. Severe nephropathy was found in about 6% of the patients. Overall prognosis of HSN is relatively good[3,7,9]. During the study period, no patient progressed to end-stage renal disease (ESRD), which suggests a good prognosis. However, long-term follow-up is needed to predict renal prognosis[13].

Laboratory tests are not diagnostic for HSP[1]. Our data showed increased ESR values in 91%, elevated CRP in 75% and leukocytosis in 25%. ESR and CRP values were higher than the Italian[7], Spanish[12] and Turkish[10] series. In the Spanish cohort[12], leukocytosis was more frequent when compared with our series. In the literature[7,12], increased serum IgA and decreased complement levels are reported in 20-50% and 10-20%, respectively. Conversely, our data showed neither decreased complement nor increased serum IgA levels, although these tests were not performed in all of the patients. Our findings for serum IgA level were similar to those of Nong and coworkers[9].

The frequency of relapses varies from series to series. Relapses occurred in 35% of Italian patients[7], in 33% of American patients[10], in 15% of Spanish patients[13], and in 7% of Turkish patients[11]. In our study group, relapses occurred in 5% of the children, within the first year.

A major matter of concern for clinicians who see children with HSP is to predict the risk of renal involvement. From the literature review[14-18], persistent purpura, severe abdominal pain, older age, corticosteroid treatment, mild renal symptoms at onset, and reduced serum coagulation factor XIII level were significantly related to the possibility of renal involvement. In

our study, the univariate analysis revealed that female sex, GI bleeding, atypical presentation, and corticosteroid treatment are significantly related to renal involvement. The multivariate analysis indicated that female sex, atypical presentation and corticosteroid treatment increased the hazard of renal involvement in children with HSP. The present study underlines for the first time the association between renal involvement and female sex or atypical presentation in HSP children. As a predictor factor for renal involvement, atypical presentation is less valuable because of the retrospective character of our study. There is considerable disagreement in the published literature regarding early introduction of corticosteroids and a reduced frequency of nephritis in HSP. Kaku et al.[15] and Mollica et al.[19] reported that corticosteroid therapy diminished the risk of renal involvement. However, Ronkainen et al.[20] showed that early prednisone treatment did not prevent the development of nephropathy, but altered the course of renal involvement. On the contrary, Huber et al.[21] found no effect of prednisone treatment in reducing renal involvement during a one-year follow-up. In our patients, we demonstrated that early use of corticosteroid was associated with greater renal involvement. However, these patients exhibited a greater frequency of severe GI involvement and, therefore, required these medications. Thus, it can be concluded that early use of corticosteroids does not alter the prognosis in HSP. Many researchers attempted to correlate renal involvement with clinical severity[7,17,18,20]. Based on the retrospective nature of our study, it is not clear whether the high risk of renal involvement in early steroid treatment is related to the severe clinical situation or the impact of the corticosteroid therapy. Further prospective studies are needed to prove the relationship between early corticosteroid usage and severe renal involvement.

In most cases, HSP is a self-limited condition that lasts four weeks on average; relapses are not uncommon[1]. In the literature, corticosteroid treatment in the acute phase[7] and persistence of the typical HSP rash for more than one month[16] were significantly correlated with relapse occurrence. In contrast, according to one study[22], no clinical or laboratory characteristics were found to be predictive of recurrence. Our statistical analyses of epidemiological, clinical and laboratory data as predictors of relapses showed that corticosteroid treatment in the acute phase was significantly correlated with recurrence.

In conclusion, HSP is a common vasculitis in childhood. In our cohort from western Turkey, the majority of the cases showed full recovery without end-stage renal failure. Renal involvement occurred in 45% of our patients. Based on our findings, female sex, atypical presentation and corticosteroid treatment were predictive factors for renal involvement. Relapses, occurring in 5% of patients, were significantly more frequent in those treated with corticosteroid. Since our patients with severe disease were more likely to be treated with corticosteroids, disease severity or corticosteroid treatment, or both, might be the risk factors for renal involvement and relapse. Therefore, the impact of early corticosteroid treatment in HSP patients should be assessed cautiously.

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