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ORIGINAL ARTICLE

Henoch-Schönlein purpura nephritis: initial risk factors and outcomes in a Latin American tertiary center

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Abstract

The objective of this study was to evaluate prevalence, initial risk factors, and outcomes in Henoch-Schönlein purpura nephritis (HSPN) patients in Latin America. Two hundred ninety-six patients (validated EULAR/PRINTO/PRES HSP criteria) were assessed by demographic data, clinical/laboratorial involvements, and treatments in the first 3 months after diagnosis. They were followed-up in a Latin American tertiary center and were divided in two groups: with and without nephritis. Persistent non-nephrotic proteinuria, nephrotic proteinuria, and acute/chronic kidney injury were also systematically evaluated at 1, 5, 10, and 15 years after diagnosis. HSPN was evidenced in 139/296 (47%) in the first 3 months. The median age at diagnosis was significantly higher in HSPN patients compared without renal involvement [6.6 (1.5–17.7) vs. 5.7 (0.9–13.5) years, $p = 0.022$]. The frequencies of persistent purpura (31 vs. 10%, $p < 0.0001$), recurrent abdominal pain (16 vs. 7%, $p = 0.011$), gastrointestinal bleeding (25 vs. 10%, $p < 0.0001$), and corticosteroid use (54 vs. 41%, $p = 0.023$) were significantly higher in the former group. Logistic regression demonstrated that the independent variables associated with HSNP were persistent purpura (OR = 3.601; 95% CI (1.605–8.079); $p = 0.002$) and gastrointestinal bleeding (OR = 2.991; 95% CI (1.245–7.183); $p = 0.014$). Further analysis of patients without HSPN in the first 3 months revealed that 29/118 (25%) had persistent non-nephrotic proteinuria and/or hematuria in 1 year, 19/61 (31%) in 5 years, 6/17 (35%) in 10 years and 4/6 (67%) in 15 years after diagnosis. None of them had chronic kidney injury or were submitted to renal replacement therapy. The present study observed HSPN in almost one half of patients in the first months of disease, and HSPN was associated with persistent purpura and gastrointestinal bleeding. One fourth of patients had nephritis only evidenced during follow-up without severe renal manifestations.

Keywords Children · Corticosteroid · Gastrointestinal bleeding · Henoch-Schönlein purpura · Immunoglobulin a vasculitis · Nephritis

Introduction

Henoch-Schönlein purpura (HSP), also named immunoglobulin A vasculitis, is the most frequent primary vasculitis affecting children and adolescents [1–7]. This disease is characterized by cutaneous, articular, gastrointestinal, and renal involvements [1–3].

Renal alterations observed in HSP nephritis (HSPN) patients are self-limited and usually with transitory microscopic hematuria and/or low-grade proteinuria in the first 3 months after diagnosis [1, 6]. HSPN may have acute, recurrent, or chronic course and is considered the main risk factor for poor outcome [6, 8–10]. Deterioration or new development of nephritis in HSP patients have been described during follow-up, generally using clinical definition of 1990 American College of Rheumatology (ACR) classification criteria studies [10–13].

In 2010, validated and international classification criteria for children and adolescents HSP patients were proposed by European League Against Rheumatism (EULAR), Paediatric Rheumatology International Trials Organisation (PRINTO)

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and Paediatric Rheumatology European Society (PRES) [14]. Data of initial risk factors associated with HSPN using EULAR/PRINTO/PRES criteria were reported by European and Asiatic HSP populations [6, 15–19], and rarely evaluating short and medium-term outcomes [19]. To our knowledge, there is no study assessing initial risk factors associated with HSPN and outcomes, using these new criteria, in a cohort of children and adolescents with this primary vasculitis in Latin America.

Therefore, the objectives of the present study were to evaluate initial risk factors associated with HSPN and outcomes in pediatric patients with HSP assessed in 1, 5, 10, and 15 years after diagnosis.

Patients and methods

Data from 322 children and adolescents with HSP followed at the Pediatric Rheumatology Department of our University Hospital during a 32-year period (January 1983 to December 2015) were retrospectively assessed. Twenty-six patients were excluded due to incomplete medical charts. The remaining 296 patients fulfilled validated EULAR/PRINTO/PRES criteria for HSP patients and were evaluated [14]. Demographic data, clinical manifestations, laboratory exams, and treatments were systematically evaluated in the first 3 months after disease diagnosis, and in 1, 5, 10, and 15 years after diagnosis. The Ethics Committee of our University Hospital approved this study, and informed consent was obtained from all patients and their legal guardians.

HSPN was defined according to the presence of hematuria (> 5 red blood cells/high power field), red blood cell casts in urinary sediment, and/or proteinuria > 0.1 g/m^2/day [1, 14]. Nephrotic syndrome was characterized by edema, serum albumin < 2.5 g/L, and proteinuria > 1 g/m^2/day [1]. High blood pressure was defined as systolic and/or diastolic blood pressures ≥ 95th percentile for gender, age, and height on ≥ 3 occasions [20]. Acute kidney injury was diagnosed by sudden increase in serum creatinine above 2 mg/dl [21] or by modified RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) [22]. Chronic kidney insufficiency was defined as structural or functional kidney abnormalities for ≥ 3 months, with decreased glomerular filtration rate < 60 ml/min/1.73 m^2 [23]. Renal replacement therapy (hemodialysis, peritoneal dialysis, hemofiltration, and renal transplantation) was also assessed. Pregnancy and/or surgery after diagnosis were evaluated as trigger factors for HSPN relapse [10, 19].

Renal biopsy was performed in HSPN patients with severe (nephrotic syndrome, acute, or chronic renal disease) and/or persistent renal alterations (hematuria or proteinuria > 0.1 g/m^2/day with > 3 months) [1]. Kidney biopsy was classified according to histological findings proposed by the International Study of Kidney Disease in Children (ISKDC): grade I (minor glomerular abnormalities), grade II (pure mesangial proliferation), grade III [minor glomerular abnormalities or mesangial proliferation, with crescents/segmental lesions (sclerosis, adhesion, thrombosis, and necrosis) in < 50% of the glomeruli], grade IV (same as grade III but with crescents/segmental lesions in 50–75% of the glomeruli), grade V (same as grade III but with crescents/segmental lesions in > 75% of the glomeruli), and grade VI [membranoproliferative-like lesions and tubulointerstitial lesions (interstitial inflammation or fibrosis and tubular loss)] [24].

HSP patients were divided in two groups: with and without HSPN at the first 3 months. Additionally, persistent non-nephrotic proteinuria, nephrotic proteinuria, and renal insufficiency were also evaluated in 1, 5, 10, and 15 years after diagnosis in two groups: patients with HSPN and HSP patients without renal involvement.

Demographic data included gender, age at diagnosis, disease duration, and body mass index (BMI). BMI was characterized by weight in kilograms divided by the square of the body height (m^2). Recurrent purpura/petechiae was defined as new cutaneous lesions after total recovery and persistent purpura/petechiae, as skin lesions persisting for ≥ 1 month [1]. Arthritis was defined by joint swelling or joint pain with limitation on motion. Arthralgia was characterized by joint pain without joint edema or limitation on motion [14], and recurrent arthritis as new arthritis after total recovery [1].

Abdominal pain was determined as diffuse abdominal colicky with acute onset, and severe abdominal pain as the presence of at least one of the following: abdominal angina, bowel intussusception, and gastrointestinal bleeding. Recurrence was defined as new abdominal pain after complete resolution. Abdominal Doppler ultrasound was performed to evaluate severe abdominal involvement [1].

Scrotal involvement was defined by the presence of scrotal edema and pain/tenderness in physical examination and/or testicular Doppler ultrasound abnormalities [25, 26]. Neuropsychiatric involvement was defined as the presence of at least one neuropsychiatric manifestation, such as headache, seizure, hemiparesis, aphasia, cortical blindness, and impaired consciousness [27].

Current HSP treatment data were also recorded: corticosteroid (prednisone, prednisolone, and/or intravenous methylprednisolone), intravenous immunoglobulin (IVIG), azathioprine, cyclosporine, intravenous cyclophosphamide (IVCYC), plasmapheresis, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockade.

Statistical analysis The sample size provided power of 80% to find differences from 10 to 13% among the groups with and without HSPN (Graphpad StatMate 1.01). Results were presented as median (range) or mean ± standard deviation (SD)

for continuous variables and number (%) for categorical variables. Mann-Whitney or *t* tests were used to compare continuous variables between the two study groups (with and without HSPN). For categorical variables, the differences were evaluated by Fisher's exact test. Multivariate analysis was carried out by Backward Stepwise logistic regression. In the regression model, the dependent variable was the presence of HSPN and the independent variables were those with 20% in univariate analysis. For all statistical tests, p value less than 0.05 were considered of statistical significance.

Results

HSPN was diagnosed in 139/296 (47%) in the first 3 months after diagnosis. Of them, isolated hematuria was observed in 19% of HSPN patients, isolated proteinuria in 47%, and both (hematuria and proteinuria) in 26%. Nephrotic syndrome was identified in 4/139 (0.03%), acute kidney injury in 5/139 (0.04%), and none had chronic kidney insufficiency. The median disease PHS duration was 2.5 years (range 0.1–15.9).

Table 1 shows demographic data, clinical/laboratorial involvements, and treatments in with and without HSPN patients in the first 3 months after diagnosis. The median age at HSP diagnosis was significantly higher in HSPN patients compared to those without this complication [6.6 (1.5–17.7) vs. 5.7 (0.9–13.5) years, $p = 0.022$]. The frequencies of persistent purpura/petechiae (31 vs. 10%, $p < 0.0001$), recurrent abdominal pain (16 vs. 7%, $p = 0.011$), gastrointestinal bleeding (25 vs. 10%, $p < 0.0001$), and corticosteroid use (54 vs. 41%, $p = 0.023$) were significantly higher in the former group. No differences were evidenced regarding male gender, BMI, arterial hypertension, increased serum IgA, IVCYC, and IVIG use in HSPN patients compared to those without renal involvement ($p > 0.05$) (Table 1).

Table 2 presents multivariate analysis by logistic regression in HSP patients in the first 3 months after diagnosis. The logistic regression model showed that only persistent purpura (OR = 3.601; 95% CI 1.605–8.079; $p = 0.002$) and gastrointestinal bleeding (OR = 2.991; 95% CI 1.245–7.183; $p = 0.014$) were associated with HSPN.

Regarding follow-up, 172/296 (58%) had HSPN during disease course. None of them had pregnancy and/or surgery, as trigger factor of nephritis. Kidney biopsies were performed in 16/172 (9%) HSP, and ISKDC histological findings showed grade I in 3/16 (19%), grade II in 12/16 (75%), and grade III in 1/16 (6%).

Regarding abnormalities at follow-up, further analysis of 139 HSP patients who presented nephritis in the first 3 months revealed that hematuria, cell cast, persistent non-nephrotic proteinuria, nephrotic proteinuria, and acute kidney injury were respectively observed in 1 year [35/88 (40%), 7/88 (8%), 46/88 (52%), 1/88 (1%), and 2/88 (2%)], in 5 years [16/47 (34%), 6/47 (13%), 25/47 (53%), 1/47 (2%), and 1/47 (2%)], in 10 years [6/20 (30%), 0/20 (0%), 9/20 (45%), 1/20 (5%), and 1/20 (5%)], and in 15 years [1/6 (17%), 0/6 (0%), 1/6 (17%), 0/6 (0%), and 0/6 (0%)]. None of them was submitted to renal replacement therapy: hemodialysis, peritoneal dialysis, and hemofiltration and/or kidney transplantation.

In addition, regarding abnormalities at follow-up in 118/157 (75%), HSP patients without initial nephritis showed renal involvement in 33/118 (28%) HSP patients during follow-up. Of them, 22/33 (67%) presented nephritis in 1 year, 8/33 (24%) in 5 years, 2/33 (6%) in 10 years, and 1/33 (3%) in 15 years. Of 118 HSP patients, 12/118 (10%) had hematuria, 4/118 (3%) cell cast, and 14/118 (12%) persistent non-nephrotic proteinuria in 1 year; 9/61 (15%) had hematuria, 2/61 (3%) cell cast, and 14/61 (23%) persistent non-nephrotic proteinuria in 5 years; 4/17 (23%) had hematuria, 2/17 (12%) cell cast, and 5/17 (29%) persistent non-nephrotic proteinuria in 10 years; and 2/6 (33%) had hematuria, 1/6 (17%) cell cast, and 3/6 (50%) persistent non-nephrotic proteinuria in 15 years after follow-up. None of them had nephrotic syndrome, acute kidney injury, and chronic renal disease and was submitted to renal replacement therapy. Angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockade was used in the majority of HSPN patients with persistent non-nephrotic proteinuria.

Discussion

The present study observed HSPN in almost one half of patients in the first 3 months after diagnosis, and HSPN was associated with persistent purpura and gastrointestinal bleeding. One fourth of patients had nephritis only evidenced during follow-up without severe renal manifestations.

One of the strengths of this study was the inclusion of a large cohort of HSP patients followed in a tertiary center of Latin America that fulfilled the validated EULAR/PRINTO/PRES criteria [14]. The medium and long-term follow-up was relevant, since nephritis may occur solely during disease course [10–12]. Moreover, the use of standardized database was also important. However, the main weaknesses of our study were the retrospective design, with potential missing data, and the absence of serum galactose IgA1 analysis [28].

At disease onset, nephritis occurred from 20 to 80% of HSP patients [1, 17, 29, 30], as observed herein. The majority of our HSP patients presented mild renal abnormalities, whereas nephrotic syndrome and acute renal injury were rarely observed at the beginning of this primary vasculitis, as also previously reported [31].

Furthermore, these findings indicated low grades of severity ISKDC classification and with the absence of renal replacement therapy in our patients. Indeed, the very low frequency of end-stage renal disease may be related to the short

Table 1 Demographic data, clinical/laboratorial involvements, and treatments in patients with and without Henoch-Schönlein purpura nephritis (HSPN) in the first 3 months after diagnosis

Variables at diagnosis, $n = 296$	With HSPN ($n = 139$)	Without HSPN ($n = 157$)	p
Demographic data			
Age at HSP diagnosis, years	6.6 (1.5–17.7)	5.7 (0.9–13.5)	0.022
Male gender	66 (47)	81 (52)	0.480
Body mass index, kg/m^2, $n = 275$	16.1 (10.6–28.4)	16.1 (11.8–32.7)	0.439
Clinical/laboratorial involvements			
Persistent purpura/petechiae, $n = 290$	42 (31)	16 (10)	< 0.0001
Recurrent purpura/petechiae, $n = 294$	38 (27)	30 (19)	0.092
Purpura/petechiae duration, days, $n = 280$	15 (2–270)	14.5 (1–82)	0.113
Arthritis/arthralgia	110 (79)	125 (80)	0.919
Recurrent arthritis/arthralgia	7 (5)	11 (7)	0.479
Arthritis/arthralgia duration, days, $n = 209$	5 (1–113)	6 (1–30)	0.678
Abdominal pain	91 (65)	91 (58)	0.185
Recurrent abdominal pain, $n = 295$	23 (16)	11 (7)	0.011
Severe abdominal pain, $n = 178$	37 (42)	25 (28)	0.059
Abdominal pain duration, days, $n = 155$	1 (1–6)	1 (1–5)	0.470
Gastrointestinal bleeding, $n = 294$	35 (25)	15 (10)	< 0.0001
Bowel intussusception	1 (1)	0 (0)	0.470
Scrotal involvement	10 (7)	18 (11)	0.210
Recurrent scrotal involvement	1 (1)	0 (0)	0.470
Scrotal involvement duration, days, $n = 20$	3.5 (2–11)	4 (1–17)	0.528
Neuropsychiatric involvement	1 (1)	0 (0)	0.470
Arterial hypertension, $n = 251$	20 (16)	19 (15)	0.676
Increased serum IgA, $n = 168$	29 (38)	38 (42)	0.589
Treatments			
Renal replacement therapy	0 (0)	0 (0)	1.000
Corticosteroid use	75 (54)	64 (41)	0.023
Immunosuppressive agents	1 (1)	0 (0)	0.469
IVIG	3 (2)	1 (1)	0.347

Results are presented as median (minimum value-maximum value) or n (%), increased serum IgA (> 255 mg/dL)
IVIG intravenous immunoglobulin

and medium period of disease follow-up. Goldstein et al. showed progressive renal insufficiency with long-term disease duration in a UK HSP population [10, 11].

We confirmed that persistent purpura and gastrointestinal bleeding were associated with HSPN in 3 months after onset using EULAR/PRINTO/PRES criteria. These results were similar to studies carried out with European and Asiatic HSP populations; however, they used non-validated HSP criteria for children and adolescents [6, 15, 32–34].

Importantly, one fourth of HSP patients without initial nephritis showed additional renal alteration at medium-term assessment. Subclinical renal abnormalities, with persistent non-nephrotic proteinuria and/or hematuria, suggested mild renal alterations. The prognosis was favorable in our patients with absence of severe renal manifestations during follow-up. This aspect may suggest different pathogenesis and genetic abnormalities in our population. Further long-term and prospective study will be necessary in Latin America to evaluate these findings.

Even mild renal abnormalities may result to chronic kidney failure after long-term follow-up [10, 35, 36]. Indeed, persistent proteinuria in adult with HSP may induce

Table 2 Multivariate analysis by logistic regression in patients with and without Henoch-Schönlein purpura nephritis (HSPN) in the first 3 months after diagnosis

Dependent variable	Independent variables	OR (CI 95%)	p
HSPN	Persistent purpura	3.601 (1.605–8.079)	0.002
	Gastrointestinal bleeding	2.991 (1.245–7.183)	0.014

CI confidence interval, *OR* odds ratio

tubulointerstitial fibrosis [37], and angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockade should be indicated in children with proteinuria [38]. A very unusual absence of chronic renal failure/end-stage kidney disease was observed in the present study during follow-up, contrasting with a systematic review that long-term renal impairment occurred in 5% of HSP patients who had abnormal urinary findings [39]. Therefore, rigorous monitoring of renal involvement should be performed during childhood and adulthood in HSP patients.

In conclusion, in the present study, initial HSPN was associated with persistent purpura and gastrointestinal bleeding. Nephritis was also evidenced during follow-up in HSP patients without severe renal manifestations; however due to retrospective nature of this study, further prospective study will be necessary.

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Compliance with ethical standards The Ethics Committee of our University Hospital approved this study, and informed consent was obtained from all patients and their legal guardians

Disclosures None.

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