Implications of upper respiratory tract infections and drugs in the clinical spectrum of Henoch-Schönlein purpura in children

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ABSTRACT

Objective. *To assess whether children with Henoch-Schönlein purpura (HSP) who had an upper respiratory tract infection (URTI) or received medication prior to the onset of the disease exhibited a different clinical spectrum of features and outcome from children without such a history.*

Methods. *Retrospective study of children (≤ 14 years old) with HSP diagnosed from 1980 through December 2001 at the single hospital for the Lugo region (Northwest Spain). Children with primary cutaneous vasculitis were classified as having HSP according to currently used criteria. Drugs or URTI were considered precipitating events if any new medication was taken or an URTI had occurred within a week prior to the onset of the vasculitis. A comparative analysis of clinical and laboratory features according to the presence or absence of URTI and drugs was conducted.*

Results. *Eighty-six children fulfilled the classification criteria for HSP. Eight of them were excluded from this analysis due to insufficient follow-up (less than 1 year post-diagnosis). An URTI and a history of drugs were reported to occur in 32/78 (41%) and 23/78 (30%) children respectively. No differences in the age at the onset of the disease, gender and seasonal incidence between children with or without URTI were observed. However, 23/32 (72%) children with URTI had hematuria with or without proteinuria, compared with only 18/46 (39%) children without history of URTI (p = 0.004). This higher incidence of renal manifestations in HSP with URTI was not associated with more severe nephritis or with a significantly higher frequency of renal sequelae or relapses of the disease. No statistically significant differences between children with or without a history of drugs were observed.*

Conclusion. *Although in unselected children with HSP a history of URTI seems to be associated with a higher incidence of nephritis, it does not influence the outcome of the disease.*

Introduction

Henoch-Schönlein purpura (HSP) is a small-sized blood vessel vasculitis due to IgA-mediated inflammation characterized by leukocytoclastic angiitis and predominant cutaneous involvement (1, 2). In at least 50% of children with HSP an upper respiratory tract infection (URTI) may precede the onset of the disease by several days or weeks (3). Pharyngitis or rhinopharyngitis and tracheobronchitis have been frequently implicated in the development of the disease. The organism most frequently isolated is the beta-hemolytic streptococcus group A (pyogenes) (3). Some drugs, especially penicillin, ampicillin, erythromycin, and non-steroidal anti-inflammatory drugs, have also been considered to be precipitating events (4).

In this study we have sought to assess whether children with HSPwho had an URTI or received medication prior to the onset of the vasculitis exhibited a different spectrum of features.

Patients and methods

Retrospective review of the case records of all patients 14 years old and younger diagnosed with primary cutaneous vasculitis in the department of Pediatrics of the Hospital Xeral-Calde (Lugo, Spain) from January 1980 through December 2001. This hospital is the reference center for almost a quarter of a million people living in the middle area of the province of Lugo (Galicia, Northwest Spain) (5, 6).

For the purpose of this study two investigators (MAG-G and MCC) reviewed all medical records. A third investigator (CG-P) reviewed 10% of the records for validation of the data abstraction. Inter-observer agreement in the classification of patients with HSP and the potential predisposing factors (URTI and drugs) and complications was assured. Classification questions were reviewed and adjudicated with two investigators (MAG-G and CG-P).

Inclusion criteria

A diagnosis of primary cutaneous vasculitis in children was accepted if they had typical non-thrombocytopenic symmetric palpable purpura involving the lower extremities. In these cases other conditions such as connective tissue diseases and infections were excluded. Children with primary cutaneous vasculitis were classified as having HSP if

they met 3 or more of the criteria proposed by Michel *et al*. (7). These criteria are the following: clinical evidence of palpable purpura, history of bowel angina, evidence of gastrointestinal bleeding, presence of hematuria (macroscopic or microscopic), age at onset of the disease ≤ 20 years, and no history of medication received prior to the onset of the vasculitis.

For the purpose of this study only those children with at least 1 year's follow-up post-diagnosis were examined.

Clinical definitions

Clinical definitions used in the present study have been described in former reports on HSP (5,6). URTI was considered to be present and related to the vasculitis if a cold, flu/influenza was described by the patient or his/her parents or rhinopharyngitis, tracheobronchitis or tonsillitis was observed by a physician within the week before the onset of the vasculitis.

Drug-intake history was considered to be a potential precipitating event of the vasculitis if any new medication was taken within a week prior to the onset of the disease.

Nephritis (renal involvement) was defined as the presence of hematuria (≥ 5 red blood cells/high power microscopic field) and/or proteinuria (> 300 mg/24 hours) that happened at any time over the whole course of the disease (5, 6).

Relapse was considered if a child diagnosed with HSP and asymptomatic for at least 1 month presented a new flare of skin lesions or other systemic complications (5,6).

Throat swab cultures were performed in some patients at the time of admission.

Statistical analysis

Student t-test was used to compare continuous variables and the chi-square test or the 2-tailed Fisher exact test for categorical variables. When a categorical variable had more than two mutually exclusive categories a p value as an overall measure of statistical significance was provided. Statistical significance was defined as $p < 0.05$. Unadjusted p values lower than 0.05 were adjusted using Finner´s method.

Table I. Epidemiological and clinical differences between HSPwith or without URTI.

		With URTI (n = 32) %		Without URTI (n = 46) %		p
Age (years)	mean ± SD	6.3 ± 3.3		6.0 ± 3.0		0.71
Sex	(male/female)	13/19		25/21		0.23
	proportion of males	41%		54%		
Seasonal pattern						0.11*
	Summer	1	3%	6	13%	
	Fall	15	47%	15	33%	
	Winter	7	22%	18	39%	
	Spring	9	28%	7	15%	
History of drugs		11	34%	12	26%	0.43
Predominant skin lesion	Palpable purpura	32	100%	46	100%	1.00
Location of skin lesions						0.19*
	Lower extremities alone	14	44%	27	59%	
	Lower extremities and trunk	6	19%	3	7%	
	Lower extremities, trunk and upper extremities	12	38%	16	35%	
Joint manifestations	Arthralgias	23	72%	33	72%	0.99
	Arthritis	20	63%	28	61%	0.88
G-I manifestations	Bowel angina	24	75%	29	63%	0.27
	Gastrointestinal bleeding	9	28%	15	33%	0.67
Renal involvement	Hematuria	23	72%	18	39%	0.004
	Proteinuria	10	31%	9	20%	0.24
	Nephrotic syndrome	3	9%	5	11%	0.83
	Renal insufficiency	0	0%	2	4%	0.51
Leukocytosis (> 11,000/mm^3)		18	56%	22	48%	0.46
Anemia Hb (< 11 g/dL)		3	9%	3	7%	0.69
High ESR (> 20 mm/1 hr)		21/29	72%	22/35	63%	0.42
High IgAserum levels		10/17	59%	10/20	50%	0.59
Positive throat cultures**		8/16	50%	1/10	10%	0.09
Relapses		7	22%	6	13%	0.30
Renal sequelae***		4	13%	4	9%	0.59

URTI: Upper respiratory tract infection. SD: Standard deviation.
G-I: Gastrointestinal: no. positive/no. tested.
*p value as an overall measure of statistical significance (for the whole distribution).
**For group Abeta-hemolytic streptococcus.
***Persistent hematuria and/or proteinuria at last follow-up (at least 1 year post-diagnosis).

Results

Between 1980 and 2001 a total of 86 children fulfilled the classification criteria for HSP. Eight of them were excluded from this analysis due to insufficient follow-up (less than 1 year). An URTI and a history of drugs were reported to occur in 32/78 (41%) and 23/78 (30%) children respectively.

Differences between HSP with or without URTI

Fifteen children had tonsillitis, 2 had tracheitis and 15 had a history of flu/influenza with pharyngitis or rhinitis. As expected, patients with a history of URTI had taken drugs prior to the diagnosis of HSP more commonly than the remaining patients (34% versus 26%). However, the difference did not reach statistical significance (Table I). No differences in the age at the onset of the disease, gender and seasonal incidence between children with or without a history of URTI were observed. It was also the case when cutaneous, gastrointestinal and articular manifestations were compared (Table I). However, 23/

32 (72%) children with URTI had renal involvement, manifested by the presence of hematuria with or without proteinuria, compared with only 18/46 (39%) children without a history of URTI (p = 0.004). Of note, when p value for hematuria/URTI relationship was adjusted using Finner´s method, it remained significant (p = 0.043).

Regardless of the presence of underlying URTI or not, all patients with renal involvement had hematuria within the first 3 months after the onset of the disease. It was microscopic in 30/41 (73%) cases and gross hematuria in 11/41 (27%). The higher incidence of renal manifestations in children with URTI was not associated with more severe nephritis or with a significantly higher frequency of relapses (Table I). Likewise, after a median follow-up of 6 years 4/32 (13%) with URTI and 4/46 (9%) without URTI persisted with hematuria (p = N.S.).

Children with a history of URTI on whom throat swab cultures were performed had more positive results for group A beta-hemolytic streptococcus (8/16 [50%]) than those without symptoms of URTI did (1/10 [10%]) (p = 0.09).

Table II. Spectrum of drugs associated with the development of HSP in 23 children (age ≤ 14 years) from the Lugo region of Northwestern Spain.

	Patients	%
Antibiotics*	13	57
Beta lactams	11	48
Amoxicillin	8	35
Penicillin G	2	9
Cephaclor	1	4
Macrolides (Erythromycin)	1	4
Metronidazole	1	4
Analgesics/NSAIDs⁺*	10	44
Paracetamol	8	35
Acetylsalicylic acid	2	9
Others	4	17
Acetylcysteine	2	9
Anti-histaminic drugs (hydroxyzine)	2	9

⁺NSAIDs: Non-steroidal anti-inflammatory drugs.
*In 4 children treatment with beta lactams and paracetamol was started at the same time.

Differences between HSPwith or without a previous history of medication

In most cases drugs taken prior to the onset of the disease were analgesics, in particular paracetamol, or antibiotics (beta lactams, generally amoxicillin) (Table II). In general, children took these drugs because of pediatrician prescription. In all cases significant quantities of the drugs were ingested before the onset of the disease and none of them had taken just one dose before the onset of the vasculitis. No statistically significant differences between children with or without drug-intake were observed (Table III).

Differences between HSPnephritis according to gender

Although in our series renal involvement was more common in females (23/40) than males (18/38) the difference was not statistically significant. Also, among these 23 females with renal involvement only 3 were older than 10 years of age and none was menstruating at or about the time of the urine examination quoted.

Discussion

There are two main limitations of this study. Firstly, its retrospective nature and, secondly, that URTI may be in

Table III. Epidemiological and clinical differences between HSPwith or without previous history of drug-intake.

		With drugs (n=23)		Without drugs (n=55)		p
Age (years)	Mean ± SD	5.2± 2.8		6.6± 3.1		0.07
Sex	Male/Female	8/15		30/25		0.11
	Proportion of males	35%		55%		
Seasonal pattern						0.10*
	Summer	0	0%	7	13%	
	Fall	9	39%	21	38%	
	Winter	6	26%	19	35%	
	Spring	8	35%	8	15%	
Predominant skin lesion	Palpable purpura	23	100%	55	100%	1.00
Location of skin lesions						0.50*
	Lower extremities alone	13	57%	28	51%	
	Lower extremities and trunk	1	4%	8	15%	
	Lower extremities, trunk and upper extremities	9	39%	19	35%	
Joint manifestations	Arthralgias	17	74%	39	71%	0.79
	Arthritis	15	65%	33	60%	0.67
G-I manifestations	Bowel angina	17	74%	36	66%	0.47
	Gastrointestinal bleeding	5	22%	19	35%	0.26
Renal involvement	Hematuria	12	52%	29	53%	0.96
	Proteinuria	3	13%	16	29%	0.16
	Nephrotic syndrome	3	13%	5	9%	0.69
	Renal insufficiency	0	0%	2	4%	1.00
Leukocytosis (>11,000/mm^3)		13	57%	27	49%	0.55
Anemia (Hb < 11 g/dL)		3	13%	3	6%	0.35
High ESR (>20 mm/1h)		12/17	71%	31/47	66%	0.73
High IgAserum levels		7/9	78%	13/28	46%	0.10
Throat cultures + **		0/6	0%	9/20	45%	0.06
Relapses		3	13%	10	18%	0.75
Renal sequelae***		2	9%	6	11%	0.59

SD: Standard deviation; G-I: Gastrointestinal no. positive/no. tested.
*Pvalue as an overall measure of statistical significance (for the whole distribution).
**For group Abeta-hemolytic streptococcus.
*** Persistent hematuria and/or proteinuria at last follow-up (at least 1 year postdiagnosis).

some cases subclinical or children may not complain about these symptoms. Thus, it is possible that some of the patients not included in this category might have also suffered a subclinical URTI. In this regard, 1 of the 10 patients without clinical manifestations of URTI on whom throat culture was taken at the time of admission yielded positive results for group A beta-hemolytic streptococcus. This finding might be due to a carrier state or to the presence of a subclinical streptococcal infection. Likewise, we cannot exclude that some of the patients who fulfilled definitions for URTI and had positive throat culture for group A beta-hemolytic streptococcus may be streptococcus carriers and in these cases the microorganism might not be the cause of the URTI. Also, a major issue always facing a study on drug-associated disease is that of causality. Such evidence is lacking for most drugs quoted in this and many other studies of vasculitis.

Most studies of pediatric HSP have found a higher incidence in boys than girls with a male/female ratio greater than 1.5 (8). However in the present series only 38/78 children were males.

Classic comprehensive reviews have indicated that a history of URTI may precede the onset of pediatric HSP in 50-70% of the cases (9, 10). As pointed out by Saulsbury (11), no single microorganism has been confirmed to be the main etiologic agent in the disease. However, in a retrospective literature review Robson and Leung described that throat swab cultures yielded positive results for beta-hemolytic streptococcus group A in 24% of 797 patients (10).

Although the long-term outcome in our patients was good, patients with URTI had renal manifestations more commonly than those without URTI did. Throat swab cultures yielded more positive results for group A beta-hemolytic streptococcus in those with URTI. This finding may support a potential role of group A beta-hemolytic streptococcus as a trigger factor in the pathogenesis of nephritis in children with HSP. In keeping with that, Masuda *et al.* have recently described the presence of group A streptococcal antigen in the glomeruli of children with HSP who developed nephritis (12). These authors confirmed the presence of mesangial deposition of nephritis-associated plasmin receptor, a group A streptococcal antigen implicated in the pathogenesis of poststreptococcal glomerulonephritis, in 10 of 33 patients with HSP nephritis. Other studies have confirmed the implication of other microorganisms associated with the development of URTI, such as Haemophilus parainfluenzae (13), in the pathogenesis of HSP nephritis.

Although absence of medication is one of the classification criteria proposed by Michel *et al.* (7), the presence of a history of medication prior to the onset of the vasculitis does not exclude a diagnosis of HSP. In this regard, 30% of children with HSP from Lugo had a history of drug intake prior to the onset of the disease. Mata-Arnaiz *et al.* reported a higher risk of renal sequelae in unselected HSP patients with previous antibiotic intake (14). However, a history of medication was not associated with worse outcome in the present series.

In conclusion, our observations suggest that a disease onset related to infectious agents may lead to a higher incidence of nephritis in children with HSP. However, it does not influence the outcome of the disease.

References

1. SAULSBURY FT: Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine (Baltimore)* 1999; 78: 395-409.
2. JENNETTE JC, FALK RP, ANDRASSY K *et al.*: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
3. FARLEY TA, GILLESPIE S, RASOULPOUR M, TOLENTINO N, HADLER JL, HURWITZ E: Epidemiology of a cluster of Henoch-Schönlein purpura. *Am J Dis Child* 1989; 143: 798-803.
4. BLANCO R, MARTINEZ-TABOADA VM, RODRIGUEZ-VALVERDE V, GARCIA-FUENTES M, GONZALEZ-GAY MA: Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum* 1997; 40: 859-64.
5. CALVIÑO MC, LLORCA J, GARCIA-PORRUA C, FERNANDEZ-IGLESIAS JL, RODRIGUEZ-LEDO P, GONZALEZ-GAY MA: Henoch-Schönlein purpura in children from northwestern Spain: a 20-year epidemiologic and clinical study. *Medicine (Baltimore)* 2001; 80: 279-90.
6. GARCIA-PORRUA C, CALVIÑO MC, LLORCA J, COUSELO JM, GONZALEZ-GAY MA: Henoch-Schönlein purpura in children and adults: clinical differences in a defined population. *Semin Arthritis Rheum* 2002; 32: 149-56.
7. MICHEL BA, HUNDER GG, BLOCH DA, CALABRESE LH: Hypersensitivity vasculitis and Henoch-Schönlein purpura: A comparison between the 2 disorders. *J Rheumatol* 1992; 19: 721-8.
8. GONZALEZ-GAY MA, GARCIA-PORRUA C: Henoch-Schönlein Purpura. *In:* BALL GV and BRIDGES SL JR. (Eds.): *Vasculitis.* NY, Oxford University Press 2002; chapter 35: 476-94.
9. NIELSEN HE: Epidemiology of Henoch-Schönlein purpura. *Acta Paedriatr Scand* 1988; 77: 125-31.
10. ROBSON WLM, LEUNG AKC: Henoch-Schönlein purpura. *Adv Pediatr* 1994; 41: 163-94.
11. SAULSBURY FT: Henoch-Schönlein purpura. *Curr Opin Rheumatol* 2001; 13: 35-40.
12. MASUDA M, NAKANISHI K, YOSHIZAWA N, IIJIMA K, YOSHIKAWA N: Group A streptococcal antigen in the glomeruli of children with Henoch-Schönlein nephritis. *Am J Kidney Dis* 2003; 41: 366-70.
13. OGURA Y, SUZUKI S, SHIRAWA T *et al.*: Haemophilus parainfluenzae antigen and antibody in children with IgA nephropathy and Henoch-Schönlein nephritis. *Am J Kidney Dis* 2000; 36: 47-52.
14. MATA-ARNAIZ C, BLANCO R, MARTINEZ-TABOADA VM, GARCIA-FUENTES M, RODRIGUEZ-VALVERDE V: Nephropathy in Henoch-Schönlein purpura: outcome and predictive factors for residual renal insufficiency. *Arthritis Rheum* 1999; 42 Suppl.: S314 (1461).