HLA-DRB1*01 Association with Henoch-Schönlein Purpura in Patients from Northwest Spain

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ABSTRACT. ***Objective.*** To examine the HLA-DRB1 phenotypes of patients with Henoch-Schönlein purpura (HSP) and determine if associations exist with disease susceptibility, clinical heterogeneity, or severe systemic complications.

Methods. A retrospective study was performed on an unselected population of patients from Northwest Spain with HSP classified according to proposed criteria. Patients were included in this study if they had at least one year of followup. Fifty Caucasian patients (25 women), 11 of them older than 20 years, were studied. Patients and ethnically matched controls were HLA-DRB1 genotyped from DNA using molecular based methods.

Results. During the course of the disease, renal manifestations, especially hematuria, and severe gastrointestinal (GI) manifestations (bowel angina or GI bleeding) were observed in more than 60% of the patients. Twenty percent of patients had persistent renal involvement (renal sequelae). Patients with HSP had a significantly higher frequency of the HLA-DRB1*01 phenotype compared to matched controls. The HLA-DRB1*07 phenotype was also significantly reduced compared with controls. Patients with severe GI manifestations or with persistent renal involvement did not exhibit any specific HLA-DRB1 association other than the underlying association with HLA-DRB1*01.

Conclusion. HSP in a population from Northwest Spain is significantly associated with HLA-DRB1*01. (J Rheumatol 2001;28:1266–70)

Key Indexing Terms:
HENOCH-SCHÖNLEIN PURPURA HLA-DRB1 DISEASE SUSCEPTIBILITY

Henoch-Schönlein purpura (HSP) is essentially a childhood disease, being the most common type of vasculitis in children and an infrequent condition in adults. Although the classic clinical triad of HSP consists of palpable purpura, joint symptoms, and abdominal pain, renal involvement constitutes the most serious complication. Infiltration of the small blood vessels with polymorphonuclear leukocytes and the presence of leukocytoclasia characterize this systemic vasculitis. Immunofluorescence staining of tissues usually reveals the presence of IgA-dominant immune deposits in the walls of the small vessels and in the renal glomeruli[1,2].

An increased familial occurrence supports a genetic predisposition for this vasculitis[3]. The genetic basis of susceptibility to HSP may be conferred by a number of gene loci, including the major histocompatibility complex (MHC). Both HSP nephritis and IgA nephropathy have been associated with deficiencies in the second and fourth components of complement encoded in the MHC Class III region and with C4 gene deletion[4-6,7]. Jin, *et al* also observed an increased frequency of HLA-DQA1*0301 in this group of patients, which suggested that both Class II and III genes could be genetic risk factors for these diseases[7].

The possible involvement of HLA Class I polymorphism in HSP has also been examined, although conflicting results have been reported. Ostergaard, *et al* failed to confirm significant association between HLA Class I molecules and HSP[8]. However, other authors showed a weak genetic association with HLA-B35 and HLA-DR4[9]. More recently, an increased susceptibility to HSP was found in Italian patients who were HLA-DRB1*01 or DRB1*11[10].

Most studies of HSP have been described from tertiary referral centers, which introduces problems associated with referral bias. To investigate this syndrome, we examined HLA-DRB1 polymorphisms in an unselected population of patients diagnosed with HSP at a single reference hospital for a defined population in Northwest Spain.

MATERIALS AND METHODS

Patients. Patients diagnosed with HSP (n = 50) were recruited from the Divisions of Pediatrics and Rheumatology of the Hospital Xeral-Calde, Lugo, Galicia, Spain. Ethnically matched controls (n = 145) were also obtained from the area surrounding Lugo. The Hospital Xeral-Calde is the only referral center for a mixed rural (60%) and urban population of nearly 250,000 people[11,12].

Inclusion criteria. IgA-dominant immune deposits affecting small vessels are frequently observed in HSP[2], and the Chapel Hill Consensus

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Conference definition of HSP is based on the presence of IgA deposits[2]. The American College of Rheumatology criteria and those put forward by Michel, *et al*, however, do not require a biopsy and IgA deposits in tissues were not examined in these studies[13,14]. As in other series[15], pediatricians from Lugo did not routinely perform skin biopsies on children with typical purpuric symmetrical palpable purpura involving the lower extremities. Also, as described in studies on cutaneous vasculitis[16], the pathologists from Lugo did not routinely perform immunofluorescence staining studies on the skin biopsies. For these reasons, the following classification criteria were used. Patients with primary cutaneous vasculitis were classified as either HSP or hypersensitivity vasculitis (HV) following the criteria proposed by Michel, *et al*[14]. Patients were classified as having HSP if they fulfilled 3 or more or of the following: (1) palpable purpura; (2) bowel angina; (3) gastrointestinal (GI) bleeding; (4) hematuria (gross or microhematuria); (5) age at onset ≤ 20 years; and (6) absence of history of medications before the onset of the disease.

Patients who met less than 3 criteria were classified as having HV and were not included in this study[14]. In addition, for the diagnosis of HSP, a primary requirement was the presence of cutaneous vasculitis involving mainly the lower extremities. In adults a skin biopsy of the cutaneous vasculitis was always required. In these patients vasculitis was diagnosed by characteristic histologic findings on skin biopsy, such as neutrophilic infiltration, leukocytoclasia, and fibrinoid necrosis into the vessel wall of arterioles, capillaries, and postcapillary venules. In children, a diagnosis of cutaneous vasculitis was considered in most cases without skin biopsy if they had typical nonthrombocytopenic symmetric palpable purpura. In these cases the diagnosis of cutaneous vasculitis had to be confirmed by an expert dermatologist. Moreover, for the diagnosis of cutaneous vasculitis in children, other conditions such as connective tissue diseases and infections, mainly infective endocarditis, AIDS, and gram negative infectious meningitis also had to be excluded. Finally, only patients with at least one year of followup were included in this study.

Clinical definitions. Following previous studies, patients older than 20 years were considered adults and those younger as children[11-14]. As reported[11,12], drug intake history and upper respiratory tract infections (URTI) prior to the onset of the disease were considered as precipitating events. They were considered present if there was a close temporal relationship (less than a week) from the start of drug intake to the onset of cutaneous vasculitis or there was a URTI shortly before the onset of cutaneous vasculitis that might explain the occurrence of this process. URTI was considered if a cold, influenza, or pharyngitis was observed within the week before the onset of skin lesions. Joint manifestations were defined if patients complained of arthralgias or peripheral arthritis was observed on examination[11,12]. For GI manifestations, bowel angina was considered present if there was diffuse abdominal pain that worsened after meals or bowel ischemia usually with bloody diarrhea. GI bleeding was defined as the presence of melena, hematochezia, or a positive test for occult blood in the stool[11,12,14]. Nephritis was defined as follows: hematuria (≥ 5 red blood cells/hpf), proteinuria (> 300 mg/24 h), nephrotic syndrome (1 g/day/m^2 body surface area or > 3.5 g/day proteinuria with plasma albumin < 25 g/l, with or without edema). Renal insufficiency was considered if the plasma creatinine concentration was above 125% the upper limit of normal[11,12,15]. Persistent renal damage, defined as renal sequelae, is an important matter of concern as it is considered to be the most common longterm complication of this disease. Persistent renal damage was considered present if after a minimum of one year's followup, patients had any of the renal complications described above.

HLA typing. DNA from patients with HSP and controls was extracted from anticoagulated blood collected in EDTA using a commercial DNA extraction kit (Bioline™). HLA-DRB1 and HLA-B phenotypes were determined using Dynal RELI™ SSO HLA-DRB and HLA-B upgraded typing kits. Reaction patterns were interpreted using Dynal software.

Statistical analysis. Continuous data were described as mean and standard deviation (mean ± SD) and categorical variables as percentages. The strength of association between HSP and HLA-DRB1 and HLA-B phenotypes was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by either chi-square test or Fisher exact analysis. Statistical significance was defined as $p \leq 0.05$. Calculations were performed with the statistical package Stata V6.

RESULTS

Clinical manifestations of patients with HSP. Thirty-nine of the 50 patients in this study were younger than 21. The main epidemiological and clinical data are shown in Table 1. As expected, a history of URTI before the onset of the vasculitis was observed in more than 50% of cases. In some of these cases drugs, especially antibiotics, were taken. Hematuria and severe GI manifestations were frequently observed. However, after a minimum of one year of followup (median 7 years) only 10 of the 50 patients had persistent renal involvement (renal sequelae), mainly hematuria.

HLA-DRB1 phenotype differences between patients with HSP and controls. When the patients were compared with matched controls, some differences in HLA-DRB1 frequencies were observed (Table 2). HLA-DRB1*01 was significantly increased in patients compared with controls (p =

Table 1. Characteristics of patients with HSP.

Groups	n (%)
Children (age < 21 yrs)	39 (78)
Adults	11 (22)
Age at the onset of the disease (yrs)	
Children	
Mean ± SD	6.2 ± 2.9
Range	2–13
Adults	
Mean ± SD	43.2 ± 2.9
Range	21–62
Sex	
Male	25 (50)
Female	25 (50)
Duration of followup (yrs)	
Median	7
Mean ± SD	8.6 ± 5.7
Drug intake history	15 (30)
History of upper respiratory tract infection	31 (62)
Palpable purpura	50 (100)
Lower extremities (alone)	19 (38)
Lower extremities and trunk	11 (22)
Lower and upper extremities and trunk	20 (40)
Arthralgias	37 (74)
Peripheral arthritis	29 (58)
Gastrointestinal bleeding	21 (42)
Bowel angina	39 (82)
Renal manifestations	
Hematuria	32 (64)
Proteinuria	18 (36)
Nephrotic syndrome	5 (10)
Renal insufficiency	1 (2)
Number of patients who required steroid therapy	20 (40)
Renal sequelae (persistent renal involvement)	10 (20)

Table 2. HLA-DRB1 phenotype frequencies in patients with HSP and controls.

HLA-DRB1	Controls (n = 145) n (%)	Cases (n = 50) n (%)
01	25 (17.2)*	17 (34)*
15 or 16	38 (26.2)	9 (18)
03	29 (20.0)	8 (16)
04	38 (26.2)	11 (22)
11 or 12	33 (22.8)	10 (20)
13	40 (27.6)	18 (36)
14	11 (7.6)	1 (2)
07	39 (26.9)**	5 (10)**
08	11 (7.6)	4 (8)
09	5 (3.4)	2 (4)
10	6 (4.1)	0 (0)

*p = 0.01; OR 2.5 (95% CI 1.2–5.1). **p = 0.01; OR 0.3 (95% CI 0.1–0.8)

0.013). In contrast, HLA-DRB1*07 phenotype was significantly reduced in the patient group (p = 0.014). HLA-DRB1 comparisons between the group of children and adults did not yield significant differences (data not shown).

HLA-DRB1 differences between patients with HSP with and without a history of URTI. As URTI have been implicated in the development of the disease, we examined whether the subgroup of patients with a history of URTI was associated with a different HLA-DRB1 association (Table 3). Patients both with and without a history of URTI shortly before the onset of the vasculitis exhibited an increased frequency of HLA-DRB1*01, although only the former reached statistical significance compared with controls. No significant differences were observed between cases with and without URTI (Table 3).

HLA-DRB1 differences between patients with HSP with and without GI manifestations. In Table 4, HLA-DRB1 phenotype frequencies in patients with GI bleeding and/or bowel angina are shown. Again, HLA-DRB1*01 was increased and HLA-DRB1*07 was decreased in patients with severe GI complications compared with controls. Although the number of patients with HSP without severe GI complications was very small (n = 9), the HLA-DRB1*01 phenotype appeared to be particularly high. However, the difference between patients with and without severe GI manifestations was not statistically significant (p = 0.13).

Table 3. HLA-DRB1 phenotype frequencies in patients with HSP with and without a history of upper respiratory tract infection (URTI).

HLA-DRB1	Controls (n = 145) n (%)	Cases With URTI (n = 31) n (%)	Cases Without URTI (n = 19) n (%)
01	25 (17.2)*	11 (35.5)*	6 (31.6)
15 or 16	38 (26.2)	5 (16.1)	4 (21.1)
03	29 (20.0)	4 (12..9)	4 (21.1)
04	38 (26.2)	7 (22.6)	4 (21.1)
11 or 12	33 (22.8)	8 (25.8)	2 (10.5)
13	40 (27.6)	10 (32.3)	8 (42.1)
14	11 (7.6)	1 (3.2)	0 (0)
07	39 (26.9)**	3 (9.7)**	2 (10.5)
08	11 (7.6)	1 (3.2)	3 (15.8)
09	5 (3.4)	1 (3.2)	1 (5.3)
10	6 (4.1)	0 (0)	0 (0)

*p = 0.02; OR 2.6 (95% CI 1.1–6.1). **p = 0.04; OR 0.3 (95% CI 0.1–1.0).

Table 4. HLA-DRB1 phenotype frequencies in patients with HSP with and without a history of severe gastrointestinal (GI) manifestations (bowel angina and/or gastrointestinal bleeding).

HLA-DRB1	Controls (n = 145) n (%)	Cases With GI (n = 41) n (%)	Cases Without GI (n = 9) n (%)
01	25 (17.2)*.**	12 (29.3)*	5 (55.6)**
15 or 16	38 (26.2)	8 (19.5)	1 (11.1)
03	29 (20.0)	6 (14.6)	2 (22.2)
04	38 (26.2)	9 (22.0)	2 (22.2)
11 or 12	33 (22.8)	9 (22.0)	1 (11.1)
13	40 (27.6)	14 (34.1)	4 (44.4)
14	11 (7.6)	1 (2.4)	0 (0)
07	39 (26.9)***	4 (9.8)***	1 (11.1)
08	11 (7.6)	4 (9.8)	0 (0)
09	5 (3.4)	2 (4.9)	0 (0)
10	6 (4.1)	0 (0)	0 (0)

*p = 0.09; OR 1.9 (95% CI 0.9–4.4). **p = 0.005; OR 6.0 (95% CI 1.6–22.2). ***p = 0.02; OR 0.3 (95% CI 0.1–0.8).

HLA-DRB1 phenotype differences between patients with HSP with and without renal manifestations. No specific HLA-DRB1 markers for the development of renal manifestations were found. HLA-DRB1*01 was significantly increased in the patients with and without renal complications compared to controls. HLA-DRB1*07 was also reduced in HSP regardless of renal involvement (Table 5). Moreover, no specific HLA-DRB1 alleles were associated with persistent renal damage (renal sequelae) (Table 5).

HLA-B phenotype differences between patients with HSP and controls. To determine a possible association between HLA-B alleles and HSP, we examined HLA-B locus polymorphism in 48 patients and 48 ethnically matched controls. There was, however, no particular HLA-B allele associated with HSP (data not shown) including HLA-B35 (21% of the cases vs 17% of controls). In addition, the association of HLA-DRB1*01 with patients with HSP was not explained by a linkage disequilibrium with HLA-B35. Thirty-four percent of the HLA-B35 negative patients exhibited HLA-DRB1*01 allele vs 10% of the HLA-B35 negative controls (p = 0.01).

DISCUSSION

The implication of HLA Class II genes in the susceptibility to systemic vasculitis has previously been described. Giant

Table 5. HLA-DRB1 phenotype frequencies in patients with HSP stratified by either renal manifestations at the onset or during the course of the disease or renal sequelae (permanent renal involvement).

HLA-DRB1	Controls	Renal Manifestations		Renal Sequelae	
		With	Without	With	Without
	(n = 145) n (%)	(n = 32) n (%)	(n = 18) n (%)	(n = 10) n (%)	(n = 40) n (%)
01	25 (17.2)[a-c]	10 (31.3)[a]	7 (38.9)[b]	3 (30.0)	14 (35.0)[c]
15/16	38 (26.2)	5 (15.6)	4 (22.2)	1 (10.0)	8 (20.0)
03	29 (20.0)	5 (15.6)	3 (16.7)	2 (20.0)	6 (15.0)
04	38 (26.2)	8 (25.0)	3 (16.7)	3 (30.0)	8 (20.0)
11/12	33 (22.8)	8 (25.0)	2 (11.1)	3 (30.0)	7 (17.5)
13	40 (27.6)	12 (37.5)	6 (33.3)	3 (30.0)	15 (37.5)
14	11 (7.6)	0 (0)	1 (5.6)	0 (0)	1 (2.5)
07	39 (26.9)[d,e]	3 (9.4)[d]	2 (11.1)	1 (10.0)	4 (10.0)[e]
08	11 (7.6)	2 (6.3)	2 (11.1)	1 (10.0)	3 (7.5)
09	5 (3.4)	2 (6.3)	0 (0)	0 (0)	2 (5.0)
10	6 (4.1)	0 (0)	0 (0)	0 (0)	0 (0)

[a]p = 0.07; OR 2.2 (95% CI 0.9–5.1); [b]p = 0.03; OR 3.1 (95% CI 1.1–8.4); [c]p = 0.01; OR 2.6 (95% CI 1.2–5.6); [d]p = 0.04; OR 0.3 (95% CI 0.1–0.9); [e]p = 0.03; OR 0.3 (95% CI 0.1–0.9).

cell arteritis (GCA), a vasculitis involving primarily large and medium-sized blood vessels, constitutes the best example. In this systemic vasculitis most studies have shown an association between HLA-DRB1*04 alleles and GCA[17–21]. Further, clinical features of severity, such as of visual complications, were also associated with HLA-DRB1*04[22]. Contradictory results have been reported for HLA associations with vasculitis involving small and medium-sized vessels such as Wegener's granulomatosis[23–30].

As for other vasculitides, there is scarce information on the implication of HLA-DRB1 in the susceptibility to HSP. We observed that regardless of renal involvement and the presence of other severe complications, HSP in Northwest Spain is associated with HLA-DRB1*01 and negatively associated with HLA-DRB1*07. These results are in keeping with those reported by Amoroso, *et al*[10]. These authors suggested that susceptibility to HSP may have a genetic basis, as in their series the presence of HLA-DRB1*01 and also HLA-DRB1*11 was more common, while HLA-DRB1*07 was less common than in their controls. Moreover, these authors did not find significant differences in HLA-DRB1 frequencies between patients with or without renal disease. In contrast to Abe, *et al*[31] and Freycon, *et al*[32], no association with HLA-DRB1*04 phenotype in this group of patients with HSP was observed.

The existence of an HLA Class II association with HSP has implications for our understanding of the etiology of this disease. Current immunological thinking would propose that an associated Class II molecule such as HLA-DRB1*01 contributes to disease by its role in presenting antigenic peptides derived from exogenous proteins to specific T cell receptors on CD4 positive cells. The HLA-DRB1*01 allele could exert disease susceptibility by exhibiting a particularly high affinity for an antigen involved in HSP. However, there is little evidence for involvement of T cells in HSP etiopathogenesis and other explanations may be more appropriate.

Linkage disequilibrium is strong between certain alleles of multiple loci within the MHC and it is possible that the HLA-DRB1*01 allele is just a marker for an HSP disease susceptibility gene elsewhere in the region. A similar explanation has recently been given for familial hemochromatosis, where the reported association with HLA-A3 was eventually found to be due to linkage disequilibrium with a disease-causing mutation in the HLA-H gene[33].

HLA-DRB1*01 and HLA-B35 are in strong linkage disequilibrium in many populations forming a conserved HLA haplotype[34]. Indeed, although HSP is a well defined syndrome characterized by small vessel cutaneous vasculitis, Glass, *et al*[35] reported an association between HLA-Bw35 and cutaneous vasculitis in the setting of other autoimmune diseases. These authors observed the presence of this allele in 5 of 19 patients with complicated cutaneous vasculitis (2 systemic lupus erythematosus, 2 rheumatoid arthritis, and one Sjögren's syndrome). However, in our population, HLA-B35 was not associated with a higher susceptibility to HSP. Of note, the association with HLA-DRB1*01 was independent of HLA-B35 status, as it was also observed in HLA-B35 negative patients.

Further, Class III region complement gene polymorphisms reported to be associated with HSP in other populations may also reflect an underlying linkage disequilibrium with a primary HSP disease gene. Further studies in HSP using multiple genetic markers across the HLA region could help resolve this issue.

Our study shows that susceptibility to HSP is associated with HLA-DRB1*01. In addition, HLA-DRB1* 07 may be

a protective allele against the development of this small vessel vasculitis. Additional studies are required to confirm the association of HSP alleles encoded in the HLA region and confirm which locus is primarily associated with disease susceptibility. It will be clinically useful to search for a genetic marker that could predict disease severity and/or longterm renal involvement.

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