

HLA-B35 Association with Nephritis in Henoch-Schönlein Purpura

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ABSTRACT. Objective. To investigate the implications of the HLA-B locus in the susceptibility to Henoch-Schönlein purpura (HSP) and determine if there are associations with renal and gastrointestinal (GI) manifestations of the disease.

Methods. A retrospective study was performed on an unselected population of patients with HSP from Northwest Spain. Forty-eight Caucasian patients (24 women), 11 of them older than 20 years, were studied. Patients and ethnically matched controls were HLA-B genotyped from DNA using molecular based methods.

Results. When patients with HSP were compared with matched controls, no differences in HLA-B frequencies were observed. No HLA-B associations with GI manifestations were observed. In contrast, an increased frequency of HLA-B35 was observed in patients with renal manifestations (10 of 31) compared to those without (0 of 17). No significant distortions in frequency were seen for any other HLA-B alleles with HSP subgroups.

Conclusion. Our results support a role of HLA-B35 in the susceptibility for nephritis in unselected patients with HSP. (J Rheumatol 2002;29:948-9)

Key Indexing Terms:

HENOCH-SCHÖNLEIN PURPURA HLA-B NEPHRITIS RENAL SEQUELAE

Henoch-Schönlein purpura (HSP) is a leukocytoclastic vasculitis due to IgA dominant immune deposits, common in children and rare in adults. Renal manifestations constitute the most serious complications and longterm morbidity and mortality in HSP are mainly due to renal involvement^{1,2}.

Susceptibility to HSP and associated clinical heterogeneity may be conferred by a number of genetic loci, including the major histocompatibility complex. An increased susceptibility to HSP was found in Italian patients who were HLA-DRB1*01 or DRB1*11³. We have also recently observed a significantly higher frequency of the HLA-DRB1*01 phenotype in patients with HSP from Northwest Spain⁴. However, patients with severe manifestations or with persistent renal involvement did not exhibit any specific HLA-DRB1 association other than the underlying association with HLA-DRB1*01. This allele is in linkage disequilibrium with HLA-B*35, HLA-B*14, and HLA-B*27 in many caucasoid populations forming conserved HLA haplotypes⁵. To investigate the implications

of the HLA-B locus in the susceptibility to HSP, we examined HLA-B polymorphisms in an unselected population of patients with this vasculitis.

MATERIALS AND METHODS

Study population. Patients diagnosed with HSP (n = 48; 24 men, 24 women) were recruited from the Divisions of Pediatrics and Rheumatology of the Hospital Xeral-Calde. Thirty-seven children (mean age 6 yrs) and 11 patients older than 20 years (mean age 43 yrs) were also included. Severe gastrointestinal (GI) manifestations (GI bleeding and/or bowel angina) were found in 37 patients. All 31 patients with renal manifestations had hematuria (> 10 red blood cells/high power field), associated with proteinuria (> 500 mg/24 h) in 17 of them. After a mean followup of 10 years (minimum 2 yrs) 9 patients had persistent renal involvement (renal sequelae) manifested by the persistence of hematuria with or without proteinuria. Renal sequelae were more common in adults, in particular in men. An adult developed chronic renal insufficiency (plasma creatinine concentration > 150% upper limit of normal). In both children and adults who developed renal sequelae nephritis occurred within the first 3 months after the onset of the disease. Relapses of the vasculitis were also more common in patients who developed renal sequelae. Ethnically matched controls (n = 48) were also obtained from the same area^{6,7}.

Inclusion criteria. Patients with primary cutaneous vasculitis were classified as HSP according to the criteria proposed by Michel, *et al*⁸. Patients were classified as having HSP if they fulfilled ≥ 3 of the following: (1) Presence of palpable purpura, (2) bowel angina, (3) GI bleeding, (4) hematuria, (5) age at onset of the disease ≤ 20 years, and (6) no medications before the onset of the disease. In adults a skin biopsy of the cutaneous vasculitis showing leukocytoclastic vasculitis was always required. In children, a diagnosis of cutaneous vasculitis was considered in most cases without skin biopsy if they had typical nonthrombocytopenic symmetric palpable purpura involving the lower extremities, and other conditions such as connective tissue diseases and infections had been excluded.

HLA typing. DNA from patients and controls was extracted from anticoagulated blood collected in EDTA using a commercial DNA extraction kit

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Table 1. HLA-B phenotype frequencies in patients with HSP stratified by manifestations (data are percentages).

HLA-B	Controls, n = 48	With GI Manifestations, n = 37	Without GI Manifestations, n = 11	With Renal Manifestations, n = 31	Without Renal Manifestations, n = 17	With Renal Sequelae, n = 9	Without Renal Sequelae, n = 39
14	10.4	18.9	18.2	22.6	11.8	22.2	17.9
27	4.2	5.4	9.1	0	17.6	0	7.7
35	16.7	14.3	9.1	32.3*	0*	44.4	15.4

*p = 0.006; OR 1.8 (95% CI 1.4–2.4).

(Bioline™). HLA-B phenotypes were determined using Dynal RELI™ SSO HLA-B upgraded typing kits. Reaction patterns were interpreted using Dynal software.

Statistical analysis. The strength of association between HSP and HLA-B phenotype was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by chi-square test or Fisher's exact analysis. Statistical significance was defined as $p \leq 0.05$.

RESULTS

When patients with HSP were compared with matched controls, no differences in HLA-B frequencies, including HLA-B35, were observed. This was also the case for both pediatric and adult cases analyzed separately (data not shown).

HLA-B locus antigen frequencies previously shown to be in linkage disequilibrium with HLA-DRB1*01 (HLA-B*35, B*14, and B*27) were examined in HSP subgroups for the presence or absence of severe GI manifestations, renal manifestations, and persistent renal involvement (renal sequelae) (Table 1). No HLA-B antigenic associations were observed with GI manifestations. In contrast, a significantly increased frequency of HLA-B35 was observed in patients with renal manifestations (10 of 31) compared to those without (0 of 17). Nevertheless, the correction of p value for the number of alleles tested yielded a p value for the HLA-B35 association with nephritis slightly out of the range of significance. No significant differences were observed for either HLA-B*14 or B*27, although the former was increased in HSP cases with renal manifestation versus those without (22.6% vs 11.8%). No significant distortions in frequency were seen for any other HLA-B alleles with HSP subgroups, with the exception of a mild increase of HLA-B18, which was raised in those cases with renal sequelae compared to those without (33.3% vs 5.1%).

DISCUSSION

Associations between HLA antigens and disease can help establish a basis for susceptibility and assist in the prediction of the outcome and clinical heterogeneity. Glass, *et al*⁹ reported an association between HLA-B35 and cutaneous vasculitis in the setting of other autoimmune diseases. In 1990, Ostergaard, *et al* observed no association between HLA-class I molecules and HSP¹⁰. Two years later, Nathwani, *et al* observed that 4 of the 5 patients with recurrent episodes of palpable purpura associated with renal involvement carried the HLA-B35 allele¹¹. In 1977,

Nyulassy, *et al* examined the distribution of HLA antigens in a group of 105 patients with various forms of glomerulonephritis¹². Of note, the HLA-B35 allele was found in 8 of 29 (27.6%) patients with glomerulonephritis secondary to HSP, compared to 29 of 314 (9.3%) in controls¹². Analysis of our data suggests that although HLA-DRB1*01 is not a marker per se for any particular clinical feature of disease phenotype⁴, this is not the case for HLA-B35, which appears to independently encode renal complications.

Additional studies in unselected series of patients are required to confirm the association of nephritis in HSP with alleles encoded inside or outside the HLA region, and confirm which locus is primarily associated with disease severity.

REFERENCES

- Gonzalez-Gay MA, Garcia-Porrúa C. Henoch-Schönlein purpura. In: Ball GV, Bridges SL, editors. Vasculitis textbook. New York: Oxford University Press; 2002:476-94.
- Saulsbury FT. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine (Baltimore)* 1999;78:395-409.
- Amoroso A, Berrino M, Canale L, et al. Immunogenetics of Henoch-Schoenlein disease. *Eur J Immunogenet* 1997;24:323-33.
- Amoli MM, Thomson W, Hajeer AH, et al. HLA-DRB1*01 association with Henoch-Schönlein purpura in patients from Northwest Spain. *J Rheumatol* 2001;28:1266-70.
- Baur MP, Danilous JA. Tables of two and three locus haplotype frequencies for HLA-A, B, C, DR, Bf and GLO. In: Terasaki PI, editor. Histocompatibility testing. Los Angeles: UCLA Tissue Typing Laboratory; 1980:994-1210.
- Gonzalez-Gay MA, Garcia-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. *Medicine (Baltimore)* 1999;78:292-308.
- Garcia-Porrúa C, Gonzalez-Gay MA. Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schönlein purpura in adults. *Semin Arthritis Rheum* 1999;28:404-12.
- 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.
- Glass D, Soter NA, Gibson D, Carpenter CB, Schur PH. Association between HLA and cutaneous necrotizing vasculitis. *Arthritis Rheum* 1976;19:945-9.
- Ostergaard JR, Storm K, Lamm LU. Lack of association between HLA and Schoenlein-Henoch purpura. *Tissue Antigens* 1990;35:234-5.
- Nathwani D, Laing RB, Smith CC, Edward N. Recurrent post-infective Henoch-Schönlein syndrome: a genetic influence related to HLA B35? *J Infect* 1992;25:205-10.
- Nyulassy S, Buc M, Sasinka M, et al. The HLA system in glomerulonephritis. *Clin Immunol Immunopathol* 1977;7:319-23.