Henoch-Schönlein Purpura and Cutaneous Leukocytoclastic Angiitis Exhibit Different HLA-DRB1 Associations

MAHSA M. AMOLI, WENDY THOMSON, ALI H. HAJEER, MARIA C. CALVIÑO, CARLOS GARCIA-PORRUA, WILLIAM E.R. OLLIER, and MIGUEL A. GONZALEZ-GAY

ABSTRACT. ***Objective.*** To examine the HLA-DRB1 genotype of patients with cutaneous leukocytoclastic angiitis (CLA), a small-sized blood vessel vasculitis limited to skin, and determine if differences exist with Henoch-Schönlein purpura (HSP), a small-sized blood vessel vasculitis with cutaneous and systemic complications.

Methods. A retrospective study was performed on an unselected population of patients from Northwest Spain with primary cutaneous vasculitis classified according to proposed criteria. Patients who fulfilled classification criteria for hypersensitivity vasculitis were included in this study if they had a biopsy proven leukocytoclastic vasculitis limited to skin and, due to this, they also met the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis definitions for CLA. Patients were included in this study if they had at least 2 years' followup. We studied 96 Caucasian patients (58 HSP, 38 CLA). Patients and ethnically matched controls (n = 145) were HLA-DRB1 genotyped from DNA using molecular based methods.

Results. No HLA-DRB1 genotype differences between patients with CLA and controls were seen. HLA-DRB1*01 was increased and HLA-DRB1*07 reduced in HSP patients compared to controls. When HLA-DRB1 genotypes of patients with CLA and HSP were compared a significant increase of HLA-DRB1*15/16 and especially of HLA-DRB1*07 was observed in the patients fulfilling definitions for CLA compared to those with HSP.

Conclusion. HSP and CLA exhibit different HLA-DRB1 genotype associations. (J Rheumatol 2002;29:945–7)

Key Indexing Terms:
HENOCH-SCHÖNLEIN PURPURA — CUTANEOUS LEUKOCYTOCLASTIC ANGIITIS
HLA-DRB1 — DISEASE SUSCEPTIBILITY

Small vessel leukocytoclastic vasculitides constitute a group of clinical syndromes characterized by predominant cutaneous involvement and a different grade of systemic manifestations. All of them share the presence of vascular inflammation and blood vessel damage with inflammation of arterioles, capillaries, and postcapillary venules. Unlike other vasculitides such as Wegener's granulomatosis, microscopic polyangiitis, or Churg-Strauss syndrome, where necrotizing vasculitis involving small and medium-sized arteries is also observed[1], cutaneous leukocytoclastic angiitis (CLA) and Henoch-Schönlein purpura (HSP) are the best example among the group of vasculitides involving exclusively small blood vessels[2].

HSP is essentially a childhood disease, being the most common type of vasculitis in children and an infrequent condition in adults. In these cases, besides typical purpuric skin lesions, joint and abdominal manifestations and renal complications are frequently observed. CLA is an isolated vasculitis limited to skin[1]. Exposure to new medications or infections is often present. Arthralgias or more rarely arthritis may be observed. Other features, however, are absent. Thus, for the diagnosis of CLA systemic involvement must be excluded[3].

Increased susceptibility to HSP was found in Italian and Spanish patients who were HLA-DRB1*01[4,5]. However, HLA-DRB1*01 was not a genetic marker for disease severity. An important insight into the relationship between HSP (as the prototype of primary cutaneous leukocytoclastic vasculitis associated with systemic manifestations) and CLA (as the paradigm of vasculitis limited to skin) may be provided by determining whether they are associated with the same HLA type. We examined the HLA-DRB1 genotype in a series of patients with CLA and compared these to patients with HSP.

From the ARC Epidemiology Unit, Manchester University Medical School, Manchester, United Kingdom, and the Divisions of Rheumatology and Pediatrics, Hospital Xeral-Calde, Lugo, Spain.

M.M. Amoli, MD; W. Thomson, PhD; A.H. Hajeer, PhD; W.E.R. Ollier, PhD, ARC Epidemiology Unit, Manchester University Medical School; M.C. Calviño, MD, Pediatrics Division; C. Garcia-Porrua, MD, PhD; M.A. Gonzalez-Gay, MD, PhD, Rheumatology Division, Hospital Xeral-Calde.

Address reprint requests to Dr. M.A. Gonzalez-Gay, Rheumatology Division, Hospital Xeral-Calde, c/ Dr. Ochoa s/n, 27004 Lugo, Spain. E-mail: miguelaggay@hotmail.com

Submitted July 19, 2001; revision accepted October 30, 2001.

MATERIALS AND METHODS

Population studied. Patients diagnosed with HSP and CLA were recruited from the Divisions of Pediatrics and Rheumatology of the Hospital Xeral-Calde, Lugo, Spain.

Patients with HSP (n = 58; 29 men and 29 women, 46 of them younger than 21 yrs; median age at onset of disease 6.5 yrs) had palpable purpura involving mainly the lower extremities. Severe gastrointestinal manifestations (gastrointestinal bleeding and/or bowel angina) were found in 44 patients. All 38 patients with renal manifestations had hematuria (> 10 red blood cells/hpf), associated with proteinuria (> 500 mg/24 h) in 20 of them. After a median followup of 8 yrs (minimum 2 yrs) 12 patients had persistent renal involvement (renal sequelae).

Patients with CLA (n = 38; 21 men and 17 women, 2 of them younger than 21 yrs; median age at onset of disease 56.5 yrs) had a maculopapular and/or purpuric rash. Apart from joint manifestations, mainly arthralgia, no systemic manifestations were observed after a median followup of 4 yrs (minimum 2 yrs).

Ethnically matched controls (n = 145) were from the same area.

Inclusion criteria. Patients with primary cutaneous vasculitis were classified as having HSP or hypersensitivity vasculitis (HV) according to the criteria proposed by Michel, *et al*[6]. In adults, a skin biopsy showing leukocytoclastic vasculitis was always required. In children with HSP (age under 21 yrs), a diagnosis of cutaneous vasculitis was considered in most cases without skin biopsy if they had typical non-thrombocytopenic symmetric palpable purpura involving the lower extremities and other conditions such as connective tissue diseases and infections had been excluded. However, in children who fulfilled classification criteria for HV, a skin biopsy showing a leukocytoclastic vasculitis was also required. In addition, in this study only patients with HV and biopsy proven small-sized blood vessel leukocytoclastic vasculitis limited to skin, with or without joint manifestations, were included. Thus, those patients with HV also fulfilled the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis definitions for CLA, as the term CLA defines an isolated cutaneous leukocytoclastic vasculitis limited to skin[1].

HLA typing. HLA-DRB1 typing was performed on DNA extracted from anticoagulated blood collected in EDTA using a commercial DNA extraction kit (Bioline™). HLA-DRB1 phenotypes were determined using a Dynal RELI™ SSO HLA-DRB upgraded typing kit and Dynal RELI™ SSO strip detection reagent kit and the Dynal Auto RELI 48 machine following the manufacturer's instructions. Reaction patterns were interpreted using Dynal software.

Statistical analysis. The association between cutaneous vasculitis and HLA-DRB1 genotypes was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined by either chi-square test or Fisher's exact analysis. Statistical significance was defined as $p \leq 0.05$.

RESULTS

No HLA-DRB1 genotype differences between patients with CLA and controls were seen (Table 1). As described, HLA-DRB1*01 was increased and HLA-DRB1*07 reduced in HSP patients compared to controls. When HLA-DRB1 genotypes of patients with CLA and HSP were compared a significant increase of HLA-DRB1*15/16 and especially of HLA-DRB1*07 was observed in the group of patients fulfilling definitions for CLA (Table 1).

Table 1. HLA–DRB1 phenotype frequencies in HSP and CLA patients and controls.

HLA–DRB1	Controls, n = 145 (%)	CLA, n = 38 (%)	HSP, n = 58 (%)
01	25(17.2)[a]	8 (21)	18 (31)[a]
15 or 16	38 (26.2)	14 (37)[b]	9 (15)[b]
03	29 (20.0)	7 (18)	10 (17)
04	38 (26.2)	7 (18)	13 (22)
11 or 12	33 (22.8)	10 (26)	14 (24)
13	40 (27.6)	8 (21)	21 (36)
14	11 (7.6)	2 (5)	1 (2)
07	39(26.9)[c]	12 (31)[d]	6 (10)[c,d]
08	11 (7.6)	4 (10)	6 (10)
09	5 (3.4)	0 (0)	2 (3)
10	6 (4.1)	2 (5)	0 (0)

[a] HSP patients compared to controls, p = 0.02; OR 2.2 (95% CI 1.1–4.4).
[b] HSP compared to CLA patients, p = 0.02; OR 0.3 (95% CI 0.1–0.8).
[c] HSP patients compared to controls, p = 0.01; OR 0.3 (95% CI 0.1–0.8).
[d] HSP compared to CLA patients, p = 0.009; OR 0.3 (95% CI 0.1–0.7).

DISCUSSION

HLA predisposition for some types of small vessel vasculitis has previously been reported. For example, Cacoub, *et al* described an association between HLA-DRB1*11 allele and the development of cryoglobulinemia and vasculitis in patients infected with hepatitis C virus[7]. However, unlike HSP or CLA, in cryoglobulinemic vasculitis medium-sized or sometimes large vessels may be involved. Further, Glass, *et al*[8] reported an association between HLA-B35, which is frequently in linkage disequilibrium with HLA-DRB1*01, and cutaneous vasculitis in the setting of other autoimmune diseases. Our study is the first to establish HLA-DRB1 genotype differences between 2 types of primary cutaneous leukocytoclastic vasculitides that specifically involve small blood vessels. According to our data, CLA has no specific HLA-DRB1 genotype associations compared to controls. Although both CLA and HSP share a similar pathologic background, that is, a leukocytoclastic vasculitis, HLA-DRB1 differences suggest a different genetic susceptibility for these conditions. However, whether these differences are important in terms of pathogenesis remains uncertain. Each of these genotype variations may represent one of the numerous factors that bear on the multifactorial determinants of pathogenesis. Thus, other genetic markers must be implicated in disease susceptibility for this type of vasculitis.

Further studies in other populations are required to confirm a different genetic susceptibility in CLA and HSP. In addition, the search for markers of disease susceptibility, possibly mediated by drugs, in patients with CLA is needed.

REFERENCES

1. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994;37:187-92.
2. Gonzalez-Gay MA, Garcia-Porrua C. Other vasculitides including small vessel vasculitis. In: Isenberg DA, Maddison PJ, Woo P, Glass D, editors. Oxford textbook of rheumatology. 3rd edition. Oxford: Oxford University Press; 2002.

3. Stone JH, Nousari HC. Essential cutaneous vasculitis: what every rheumatologist should know about vasculitis of the skin. Curr Opin Rheumatol 2001;13:23-34.
4. Amoroso A, Berrino M, Canale L, et al. Immunogenetics of Henoch-Schoenlein disease. Eur J Immunogenet 1997;24:323-33.
5. 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.
6. 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.
7. Cacoub P, Renou C, Kerr G, et al. HLA-DR phenotypes influence the risk of hepatitis C virus-associated mixed cryoglobulinemia [abstract]. Arthritis Rheum 2000;43 Suppl:S1911.
8. Glass D, Soter NA, Gibson D, Carpenter CB, Schur PH. Association between HLA and cutaneous necrotizing venulitis. Arthritis Rheum 1976;19:945-9.