Polymorphism at Codon 469 of the Intercellular Adhesion Molecule-1 Locus Is Associated with Protection Against Severe Gastrointestinal Complications in Henoch-Schönlein Purpura

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ABSTRACT. ***Objective.*** Henoch-Schönlein purpura (HSP) is a small sized vasculitis affecting mainly children. Intercellular adhesion molecule-1 (ICAM-1) gene polymorphisms have recently been implicated in the susceptibility to some vasculitides. To further investigate the clinical implication of ICAM-1 polymorphisms in HSP, we examined their potential association and influence in the development of severe complications in an unselected series of patients with HSP.

Methods. Fifty-two patients, of which 41 were children, were diagnosed with HSP using classification criteria of Michel, *et al* at the Hospital Xeral-Calde (Lugo, Spain); 129 ethnically matched controls were included. Patients had at least one year of followup. Patients and controls were genotyped by allelic oligonucleotide techniques for ICAM-1 polymorphism at codon 241 and 469.

Results. The frequency distribution of the alleles and genotypes for each ICAM-1 polymorphism did not show significant differences between HSP patients and controls. Also, no differences between patients with or without renal manifestations were found. However, the frequency of the codon 469 K/E genotype was significantly decreased in patients without severe gastrointestinal manifestations compared to those with them (22.29 vs 65%, OR 0.1, p = 0.02, after correction for age, sex, and disease duration). None of the 11 adults exhibited the R/G genotype at codon 241 compared with 7 of 41 children (OR 0.0, 95% CI 0.0–2.9, p = 0.14). Patients with the R/G genotype were associated with low incidence of renal manifestations and none developed permanent renal involvement (renal sequelae); however, this finding did not achieve statistical significance.

Conclusion. ICAM-1 polymorphisms alone are not associated with development of HSP, but patients not carrying the codon 469 K/E genotype are at decreased risk of developing severe gastrointestinal complications. The R/G polymorphism at codon 241 may reduce the risk of renal sequelae in the development of HSP in adulthood. (J Rheumatol 2001;28:1014–8)

Key Indexing Terms:
HENOCH-SCHÖNLEIN PURPURA VASCULITIS ICAM-1 POLYMORPHISM
GASTROINTESTINAL COMPLICATIONS BOWEL ANGINA RENAL SEQUELAE

Henoch-Schönlein purpura (HSP) is the most common vasculitis in children and an infrequent condition in adults[1]. Infiltration of the small blood vessels with polymorphonuclear leukocytes and the presence of leukocytoclasia are typical histologic findings. Immunofluorescence staining of tissues usually reveals the presence of IgA dominant immune deposits in the walls of the small vessels (i.e., capillaries, venules, or arterioles) and in the renal glomeruli[2,3]. Although the classic clinical triad of HSP consists of palpable purpura, joint symptoms, and abdominal pain, renal involvement constitutes the most serious complication.

The genetic basis of susceptibility to HSP may be conferred by the interaction of a number of genetic loci. In this regard, a genetic association with HLA-DRB1*01 and DRB1*11 phenotypes has been reported[4]. Also, HSP has been associated with deficiencies in the second and fourth components of the complement pathway and with deletion of C4 genes[5-7].

Genetic polymorphisms in endothelial cell adhesion molecules for leukocytes have been implicated in the susceptibility to diseases that have an inflammatory component. Two coding region polymorphisms have been

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identified for intercellular adhesion molecule-1 (ICAM-1): G or R at codon 241 and K or E at codon 469[8]. Genetic polymorphisms in the ICAM-1 molecule have been shown to be involved in the susceptibility to other vasculitides such as giant cell arteritis (GCA) and Behçet's disease[9,10]. However, possible evidence of ICAM-1 polymorphisms and HSP susceptibility has not been reported. To investigate this syndrome, we examined the ICAM-1 polymorphism associations in an unselected population of patients diagnosed with HSP at the single reference hospital for a defined population in Northern Spain.

MATERIALS AND METHODS

Population studied. The study group comprised 52 patients diagnosed with HSP at the Divisions of Pediatrics and Rheumatology of the Hospital Xeral-Calde (Lugo, Northwest Spain) and 129 ethnically matched controls from the same area. The Hospital Xeral-Calde is the only referral center for a mixed rural (60%) and urban stable population of almost 250,000 people. Information about this population has been described[11,12].

Inclusion criteria. The Chapel Hill Consensus Conference definition of HSP is based on the presence of IgA deposits[3], as IgA dominant immune deposits affecting small vessels are frequently observed in HSP[2]. In contrast, the American College of Rheumatology criteria and the Michel, *et al* criteria do not require a biopsy, and IgA deposits in tissues were not examined in these studies[13,14]. In some series of HSP in children skin biopsy was not a prerequisite for the diagnosis of HSP[15]. Similarly, pediatricians from Lugo did not routinely perform skin biopsies on young children with typical purpuric symmetrical palpable purpura involving buttocks and legs. As in other studies reported for systemic vasculitis[16], the pathologists from Lugo did not routinely undertake immunofluorescence-staining studies on the skin biopsies. For these reasons we used the following classification criteria.

Patients with primary cutaneous vasculitis were classified as either HSP or hypersensitivity vasculitis following criteria of Michel, *et al*[14]. They were classified as having HSP if they fulfilled 3 or more of the following criteria: (1) Palpable purpura, (2) bowel angina, (3) gastrointestinal (GI) bleeding, (4) hematuria (gross or microhematuria), (5) age at onset ≤ 20 years, and (6) no previous history of medications before onset of disease.

Patients who met fewer than 3 criteria were classified as having hypersensitivity vasculitis and consequently were not included in this study[14]. For the diagnosis of HSP we also required presence of cutaneous vasculitis involving mainly the lower extremities. In adults a skin biopsy of the cutaneous vasculits was required. These patients were 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 non-thrombocytopenic symmetric palpable purpura involving the lower extremities. In all these cases the diagnosis of cutaneous vasculitis was confirmed by a dermatologist. In children, other conditions that may present with cutaneous lesions such as connective tissue diseases and infections, mainly infective endocarditis, AIDS, and gram negative infectious meningitis, were excluded. For the purpose of examining the outcome of HSP, in this study only patients with at least one year of followup were included.

Clinical definitions. As reported, patients older than 20 years were considered adults and those younger than this age as children[11-14]. Drug intake history and upper respiratory tract infections (URTI) before the onset of the disease were considered as precipitating events[11,12]. They were considered to be present if there was a close temporal relationship (less than a week) from the start of drug intake to the onset of vasculitis, or there was URTI shortly before onset of cutaneous vasculitis that might explain the occurrence of this process. URTI was considered to have occurred if a cold, flu/influenza, or pharyngitis was observed within the week before onset of skin lesions. Joint manifestations were recorded if patients complained of arthralgias, or peripheral arthritis was observed on examination[12]. Severe GI manifestations: Bowel angina was considered to be 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)[11,12,15]. 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 concern as it is considered the most common longterm complication of this disease. The presence of renal sequelae (persistent renal damage) was considered present if after a minimum of one year followup patients had any of the renal complications described above.

Molecular analysis of ICAM-1. (1) The first amino acid polymorphism, substitution of arginine (R) for glycine (G) at codon 241, was examined as follows: A polymerase chain reaction (PCR) assay was designed to detect single nucleotide polymorphism. The single base change G to A at codon 241 does not introduce or abolish a restriction site. We therefore mutated the forward primer by one base pair (G or T) to introduce the restriction site for the enzyme *Bsr*GI.

Forward 5' CCG TGG TCT GTT CCC TGT AC3'
Reverse 5' GAA GGA GTC GTT GCC ATA GG 3'

*Bsr*GI digested the PCR product only when the mutant A allele was present, yielding DNA fragments of 90 and 20 base pairs. A total of 100 ng genomic DNA was amplified in a 25 μl PCR reaction containing 1 × NH_4 buffer (Bioline), 2.5 mM $MgCl_2$, 0.2 mM dNTP (Bioline), 5 pmol of each primer, 0.5 U Taq polymerase (Bioline), and 1 mM betaine (Sigma). The DNA was denatured at 95°C for 2 min followed by 35 cycles of 95°C for 45 s, 50°C for 45 s, and 72°C for 45 s. The final extension was carried out at 72°C for 2 min. The presence of product (110 base pairs) was verified on a 2% agarose gel stained with ethidium bromide. PCR products were digested with *Bsr*GI in a 15 μl final volume. This contained 7 μl PCR product, 1 × NE buffer, 1 × BSA, and 5 U *Bsr*GI. The digest was incubated overnight at 37°C and the products were then visualized on a 3% agarose gel stained with ethidium bromide. (2) The second amino acid polymorphism, substitution of lysine (K) for glutamic acid (E) at codon 469, was examined using the following primers for the amplification of the region:

Forward 5'-AGG ATG GCA CTT TCC CAC T-3'
Reverse 5'-GGC TCA CTC ACA GAG CAC AT-3'

The PCR was carried out in a volume of 25 μl containing 100 ng of genomic DNA, 10 × KCl buffer (Bioline), 3.5 mM $MgCl_2$, 0.2 mM dNTPs (Bioline), 5 pmol of each primer, 1 unit of Taq DNA polymerase (Bioline), and 4 mM betaine (Sigma). The DNA was denatured at 95°C for 5 min, and temperature cycling was set at 95°C for 45 s, 56°C for 45 s, and 72°C for 45 s for 40 cycles, followed by a final extension at 72°C for 2 min. Analysis of the PCR product was performed by enzyme digestion using *Bsr*UI (New England Biolab), which cuts the product from the E469 allele and yields 2 fragments of 106 bp and 34 bp for homozygous (EE) allele but does not cut the K469, and yields one fragment of 140 bp for homozygous (KK) allele. The digestion was incubated overnight at 37°C and the products were then visualized on 3% agarose gel stained with ethidium bromide.

Statistical analysis. Strength of association between HSP and alleles or genotypes of ICAM-1 was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by either chi-square or Fisher exact analysis. The same methods were used to examine the strength of association between HSP subgroups (with renal or severe GI complications or with renal sequelae) and ICAM-1 polymorphisms. Where appropriate, correction for multiple testing was carried out using Holm's procedure. Logistic regression analysis was also used to correct for age, sex, and disease duration. All

analyses were carried out using the Number Cruncher Statistical Package for Windows (NCSS v.6.0.4), or the PEPI software package (v. 2.0) for epidemiologic analysis.

RESULTS

Clinical characteristics of patients with HSP. Forty-one children and 11 adults were included in this study. The main epidemiological and clinical data are shown in Table 1. A history of upper respiratory tract infections prior to the onset of vasculitis, frequently associated with drug intake (mainly antibiotics), was common. Joint manifestations were especially frequent in children. Renal involvement, especially hematuria, and GI manifestations occurred in more than 50% of the patients. However, at the end of this study only 10 patients had persistent renal involvement (renal sequelae), most of them hematuria.

Allele and genotype frequencies of ICAM-1 polymorphisms at codon 241 and 469. The frequencies of alleles and genotypes for each ICAM-1 polymorphism in the whole group of HSP patients were compared to those of controls. No significant differences in frequency were found between the patients and controls (Table 2).

Allele and genotype frequencies of ICAM-1 polymorphisms in patients with renal or severe GI manifestations. Frequency distribution of the alleles and genotypes for each ICAM-1 polymorphism in HSP patients with renal or severe GI manifestations was compared to that of HSP patients without complications (Table 3). No significant differences were found between patients with and without renal manifestations, but patients without severe GI complications showed a decreased frequency of the codon 469 K/E genotype compared to those with GI manifestations (OR 0.15, 95% CI 0.02–0.95, p = 0.016). This was still significant after correction for multiple testing in this group (p = 0.048). When adjusted for age, sex, and disease duration by logistic regression analysis, OR decreased to 0.1 (p = 0.02).

Allele and genotype frequencies of ICAM-1 polymorphisms in Spanish HSP patients with renal sequelae. The frequencies of alleles and genotypes for each ICAM-1 polymorphism in HSP patients with and without renal sequelae were compared. No significant differences were found (Table 4). However, none of the 11 adults exhibited the R/G genotype at codon 241 compared with 7 of 41 children, although this did not achieve significance (OR = 0.0, 95% CI 0.0–2.9, p = 0.14). In addition, the R/G genotype was associated with a low incidence of renal manifestations and no patient carrying this genotype developed permanent renal involvement (renal sequelae), although again this did not achieve statistical significance (OR = 0.0, 95% CI 0.0–3.4, p = 0.16).

DISCUSSION

Intercellular adhesion molecule-1 polymorphism has been implicated in polygenic diseases such as ulcerative colitis or multiple sclerosis[17,18]. Also, ICAM-1 genetic polymor-

Table 1. Epidemiological data and clinical manifestations in 52 patients with Henoch-Schönlein purpura (HSP).

Age at disease onset, yrs	
All patients	
Range	2–62
Median	6.5
Mean ± SD	13.7 ± 16.0
Children (n = 41)	
Range	2–13
Mean ± SD	6.1 ± 2.9
Adults, n = 11	
Range	21–62
Mean ± SD	43.2 ± 12.9
Men/women, n	25/27
Duration of followup, yrs	
Range	1–20
Median	7
Mean ± SD	8.6 ± 5.6
Drug intake history (%)	15 (28.8)
History of URTI (%)	32 (61.5)
Palpable purpura (%)	52 (100)
Lower extremities alone	21 (40.4)
Lower extremities and trunk	11 (21.2)
Lower and upper extremities and trunk	20 (38.5)
Arthralgias (%)	39 (75.0)
Peripheral arthritis (%)	31 (59.6)
Gastrointestinal bleeding (%)	21 (40.4)
Bowel angina (%)	40 (76.9)
Hematuria (%)	32 (61.5)
Proteinuria (%)	19 (36.5)
Nephrotic syndrome (%)	5 (9.6)
Renal insufficiency (%)	1 (1.9)
Number of patients who required steroid therapy (%)	20 (38.5)
Renal sequelae [persistent renal involvement] (%)	10 (19.2)

URTI: upper respiratory tract infection.

Table 2. Allele and genotype frequencies (%) of ICAM-1 polymorphisms at codons 241 and 469 in Spanish patients with HSP compared with controls.

	Controls	HSP
Codon 241		
Alleles	(2n = 258)	(2n = 104)
R	8.1	6.7
G	91.9	93.3
Genotypes	(n = 129)	(n = 52)
RR	1.5	0.0
GG	85.3	86.5
RG	13.2	13.5
Codon 469		
Alleles	(2n = 258)	(2n = 100)
K	52.5	53.0
E	47.5	47.0
Genotypes	(n = 129)	(n = 50)
KK	23.9	24.0
EE	18.8	18.0
KE	57.2	58.0

Table 3. Allele and genotype frequencies (%) of ICAM-1 polymorphisms at codons 241 and 469 in Spanish patients with HSP with renal and severe gastrointestinal (GI) manifestations. Frequency distribution of the alleles and genotypes for each ICAM-1 polymorphism in HSP patients with renal or severe GI manifestations were compared to that of HSP patients without these complications by chi-squared tests.

	Renal Manifestations		GI	
	With	Without	With	Without
Codon 241				
Alleles	(2n = 64)	(2n = 40)	(2n = 84)	(2n = 20)
R	4.7	10.0	7.1	5.0
G	95.3	90.0	92.9	95.0
Genotypes	(n = 32)	(n = 20)	(n = 42)	(n = 10)
RR	0.0	0.0	0.0	0.0
GG	90.6	80.0	85.7	90.0
RG	9.4	20.0	14.3	10.0
Codon 469				
Alleles	(2n = 64)	(2n = 36)	(2n = 82)	(2n = 18)
K	53.1	52.3	52.4	55.6
E	46.9	47.2	47.6	44.4
Genotypes	(n = 32)	(n = 18)	(n = 41)	(n = 9)
KK	25.0	22.2	19.5	44.4
EE	18.8	16.7	14.6	33.3
KE	56.2	61.1	65.9	22.2*

*OR = 0.15 (95% CI 0.02–0.95) p = 0.016 (p = 0.048 after correction for multiple testing by Holm's procedure) (vs HSP patients with GI manifestations).

Table 4. Allele and genotype frequencies (%) of ICAM-1 polymorphisms at codons 241 and 469 in Spanish patients with HSP with renal sequelae. Frequency distribution of the alleles and genotypes for each ICAM-1 polymorphism in HSP patients with renal sequelae were compared to that of HSP patients without renal sequelae by chi-squared tests. No significant differences were found.

	Renal Sequelae	
	With	Without
Codon 241		
Alleles	(2n = 20)	(2n = 84)
R	0.0	8.3
G	100	91.7
Genotypes	(n = 10)	(n = 42)
RR	0.0	0.0
GG	100	83.4
RG	0.0	16.6
Codon 469		
Alleles	(2n = 20)	(2n = 80)
K	55.0	52.5
E	45.0	47.5
Genotypes	(n = 10)	(n = 40)
KK	20.0	25.0
EE	10.0	20.0
KE	70.0	55.0

phisms have been associated with the occurrence of chronic allograft rejection[19]. In patients with GCA, vasculitis involving mainly large and medium size vessels, ICAM-1 is highly expressed in the adventitial microvessels and neovessels within inflammatory infiltrates of patients with GCA[20]; and changes in concentrations of circulating soluble ICAM-1 have been correlated with disease activity[21]. Salvarani, *et al* described a higher frequency of the allele R at codon 241 in patients with polymyalgia rheumatica and GCA[9]. We examined whether ICAM-1 genetic polymorphisms were implicated in the development and severity of HSP, a primary small sized vasculitis.

Although no differences in genotype frequency were found between patients and controls, we found that there was a significantly decreased risk of developing severe GI complications in patients not carrying the codon 469 K/E genotype. Based on those findings, patients carrying the 469 K/E genotype could be closely monitored, and early corticosteroid therapy might be considered to avoid GI complications in these patients.

The 469 polymorphism occurs in exon 6 of the ICAM-1 gene that encodes a region in the fifth immunoglobulin-like domain of ICAM-1[8]. The functional significance of this polymorphism is unknown at present, although it could potentially lead to alterations in binding, and/or costimulatory activity of the ICAM-1 molecule. Similarly, the functional influence of the R/G polymorphism at codon 241 remains unclear, although this region (in exon 4) is in the functionally important domain III of ICAM-1, which contains the binding site for the leukocyte integrin, Mac-1.

The absence of the R/G genotype at 241 codon in adults suggests that this genotype may have a protective role against the development of HSP beyond childhood age. However, the difference was not statistically different. This may be due to the small number of adults (n = 11) examined, and additional studies with increased numbers of adult patients are needed to confirm this finding. The lack of R/G genotype in patients with persistent renal involvement also suggests a protective effect of this allele against renal sequelae of the disease. However, it was not possible to provide an estimate of risk of developing this complication in patients with the R/G genotype since none of these developed this complication. Again, studies involving larger numbers of patients are needed to determine the significance of this finding.

In conclusion, ICAM-1 polymorphisms alone do not appear to be associated with incidence or severity in unselected patients with HSP in Northwest Spain, but the G/R polymorphism at codon 241 may have a protective effect on the development of HSP in adults and in the occurrence of permanent renal involvement. Also, patients without K/E genotype appear to have a reduced risk of developing severe GI complications. Further studies are required to confirm this observation in other population groups.

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