Intercellular Adhesion Molecule-1 Polymorphisms in Korean Patients with Behcet’s Disease

INTRODUCTION

Behcet’s disease (BD) is a chronic and multisystemic inflammatory disease of multifactorial etiology, involving both infectious and genetic factors (1). The clinical major symptoms of BD in Korean patients are oral ulcers (98.8%), skin lesions (84.3%), genital ulcers (83.2%), ocular lesions (50.9%), and minor symptoms including articular symptoms (38.4%), gastrointestinal symptoms (7.3%), neurological symptoms (4.6%), epididymitis (0.6%), and vascular symptoms (1.8%) (2). This wide range of clinical symptoms of BD probably reflects different genetic backgrounds.

Intercellular adhesion molecule-1 (ICAM-1, CD54) is expressed on endothelial cells and various other cells and its expression is increased during inflammation. ICAM-1 is a member of the immunoglobulin superfamily and is a ligand of macrophage-1 antigen (Mac-1; CD11b/CD18) and lymphocyte function associated antigen-1 (LFA-1; CD11a/CD18) (3). It is also involved in leukocyte migration into sites of inflammation and T-cell receptor-mediated activation of resting T cells (4).

ICAM1 gene (OMIM 147840) is located on chromosome 19p13.3-13.2 with polymorphisms of K29M, G241R, K469E, A496T, and G1838A in the 3’UTR (5, 6). Single base polymorphisms causing amino acid substitutions were identified for ICAM1 at codon 241 in exon 4 (GGG→AAG; Gly→Arg) for the Ig-like domain 3, the binding site of Mac-1, and at codon 469 in exon 6 (AAG→GAG; Lys→Glu), which codes for the Ig-like domain 5 (7). BD patients were evaluated for the levels of both soluble and tissue ICAM-1 and it has been hypothesized that the two mutations, G241R and K469E, result in more effective binding of ICAM1 to Mac-1 and LFA-1, thereby enhancing the inflammatory response (8). Both Mac-1 and LFA-1 binding site mutations might be involved in some of the inflammation events responsible for BD. While the pathogenic role of these polymorphisms is unknown, an association has been found with inflammatory diseases such as Behcet’s disease in Jordanian or Palestinian populations (9), giant cell arteritis (10), rheumatoid arthritis (11), inflammatory bowel disease (12), and chronic renal allograft failure (13).

In this study, we investigated whether ICAM1 gene polymorphisms in Korean BD patients are associated with different clinical subsets of BD.

MATERIALS AND METHODS

Patients with BD were recruited from the Behcet’s Disease specialty clinic of Severance Hospital, Yonsei Universi-
A total of 197 patients with BD and 248 healthy controls without BD were enrolled. The diagnosis of BD was made according to the established clinical criteria of the International Study Group Behcet’s Disease (14) and the revised Shimizu’s classification (15). After obtaining informed consent, blood samples were collected and genomic DNA was extracted from peripheral blood leukocytes with a QiaAmp Blood kit (Qiagen, Valencia, CA, U.S.A.).

The ICAM1G241R polymorphism was detected by BsrGI PCR-RFLP (New England Biolabs, Beverly, MA, U.S.A.) (16, 17). The ICAM1K469E polymorphism was analyzed by BstUI PCR-RFLP (New England Biolabs, Beverly, MA, U.S.A.) (17, 18).

For statistical analysis of the data, the SAS program (v 8.0e) was used.

### RESULTS

The distribution of the ICAM1469*E polymorphism differed significantly between patients and healthy controls. The frequency of both genotypes ICAM1469*K/*K and ICAM1469*E/*E was significantly higher in BD patients than in controls (66.0% vs 52.4%, \( p = 0.004 \), OR = 1.28, 95% CI 1.08-1.50). The genotype and allele frequencies of ICAM1469E in patients and in controls are shown in Table 2. The frequency of ICAM1469*E was higher in patients with skin lesions (0.41), genital ulcers (0.41), vasculitis (0.43), ocular lesions (0.41), and arthritis (0.39) than in controls (0.31). The disease duration, age at onset of BD, sex distribution, duration of follow-up, and the use of drugs did not differ between both genotypes of patients carrying ICAM1469E.

Only one heterozygote ICAM1241G/R was detected in BD patients and the ICAM1241*E mutation was not found among healthy Korean controls. The heterozygote was found in a 56-yr old man with a 12-yr history of the disease who presented with ocular lesions and had a genotype of ICAM1469*E. Our results show that the ICAM1469*E polymorphism is associated with BD, whilst the ICAM1241*E polymorphism is rare among Koreans.

### DISCUSSION

Association between ICAM1 gene mutations and BD depends on ethnic origins (Table 3). The frequency of ICAM-1469*E was higher in Korean patients with BD than in controls, Palestinians, and Jordanians, while the frequency of ICAM1241*R was higher in Italians (9, 19). The ICAM1 gene has also been associated with rheumatoid arthritis (RA) in Italian patients. ICAM1241R was associated with RA.

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**Table 1.** Demographic and clinical features of Korean patients with BD

|                      | Female/Male | No. (% ) |
|----------------------|-------------|----------|
| Female/Male          | 96/101      | (49/51)  |
| Mean age ±SD         | 40 ± 10 yr  |          |
| Mean disease duration ±SD | 11 ± 7 yr  |          |
| Major symptoms       |             |          |
| Oral ulcers          | 96/101      | 197 (100.0) |
| Skin lesions         | 88/98       | 186 (94.4) |
| Genital ulcers       | 87/80       | 167 (84.6) |
| Ocular lesions       | 74/77       | 151 (76.6) |
| Minor symptoms       |             |          |
| Arthritis            | 57/57       | 114 (57.9) |
| Vasculitis           | 4/40        | 44 (22.3) |
| Central nervous system | 7/4        | 11 (5.6)  |
| Gastrointestinal lesions | 4/7       | 11 (5.6)  |

**Table 2.** Genotype and allele frequencies of ICAM1K469E in Korean patients with BD and in controls

|                     | *K/*K (%) | *K/*E (%) | *E/*E (%) | *E | \( p \) value | OR | 95% CI   |
|---------------------|-----------|-----------|-----------|---|-------------|----|----------|
| Controls            |           |           |           |   |             |    |          |
| All patients        | 248       | 118 (47.6)| 107 (43.1)| 23 (9.3)| 0.31        |    |          |
| skin lesions        | 197       | 67 (34.0)| 100 (50.8)| 30 (15.2)| 0.41        | 0.004 | 1.28 | 1.08-1.50 |
| without             | 116       | 61 (32.8)| 96 (51.6)| 29 (15.6)| 0.41        | 0.002 | 1.29 | 1.10-1.52 |
| genitai ulcers      | 167       | 56 (33.5)| 84 (50.3)| 27 (16.2)| 0.41        | 0.004 | 1.26 | 1.08-1.47 |
| without             | 30        | 11 (36.7)| 16 (53.3)| 3 (10.0)| 0.35        | 0.002 | 1.89 | 1.26-2.86 |
| ocular lesions      | 151       | 50 (33.1)| 78 (51.6)| 23 (15.2)| 0.41        | 0.001 | 1.30 | 1.12-1.52 |
| without             | 46        | 17 (34.8)| 22 (50.0)| 7 (15.2)| 0.40        | ns   |          |
| vasculitis          | 44        | 14 (31.8)| 22 (50.0)| 8 (18.2)| 0.43        | 0.053 | 1.10 | 1.00-1.21 |
| without             | 153       | 53 (34.6)| 78 (51.0)| 22 (14.4)| 0.40        | 0.011 | 1.22 | 1.05-1.42 |
| arthritis           | 114       | 38 (33.3)| 63 (55.3)| 13 (11.4)| 0.39        | 0.011 | 1.20 | 1.05-1.38 |
| without             | 83        | 29 (34.9)| 37 (44.6)| 17 (20.5)| 0.43        | 0.045 | 1.14 | 1.01-1.29 |
| CNS                 | 11        | 6 (54.5)| 4 (36.4)| 1 (9.1) | 0.27        | ns   |          |
| without             | 186       | 61 (32.8)| 96 (51.6)| 29 (15.6)| 0.41        | 0.002 | 1.29 | 1.10-1.52 |
| gastrointestinal    | 11        | 2 (18.2)| 7 (63.6)| 2 (18.2)| 0.50        | ns   |          |
| without             | 186       | 65 (34.9)| 93 (50.5)| 28 (15.1)| 0.40        | 0.008 | 1.25 | 1.06-1.46 |

CNS, central nervous system.

\( p \) value, patients with ICAM1469*E positive vs controls with ICAM1469*E positive; OR, odds ratio; CI, confidence interval; ns, not significant.
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Table 3. Allele frequencies of ICAM1241*R and ICAM1469*E among BD patients from different populations

| Allele frequency | p value | Reference |
|------------------|---------|-----------|
| Patients with BD | Controls |
| Korean           |         |           |
| 241*R            | 0.003   | 0.000     | ns |
| 469*E            | 0.410   | 0.310     | 0.003 |
| Jordanian or     | 9       |           |
| Palestinian      |         |           |
| 241*R            | 0.012   | 0.015     | ns |
| 469*E            | 0.476   | 0.383     | 0.046 |
| Italian          | 19      |           |
| 241*R            | 0.115   | 0.031     | 0.0001 |
| 469*E            | 0.439   | 0.439     | ns |

*p value, patients vs controls; ns, not significant.

but the allele and phenotypic frequencies of ICAM1469E did not differ significantly between RA patients and the control group in the Italian study (11). The different results might be due to different genetic backgrounds. The frequency of ICAM1241*R showed a population variation in contrast to the frequency of ICAM1469*E. The frequency of ICAM1469*E is high in various countries (0.310-0.510). While ICAM1241*R is quite rare in most populations, the frequency of ICAM1241*R is higher in Europeans (0.031-0.180) (10, 13, 16, 20) compared to in Koreans and Japanese (0.000) (21) and Palestinians and Jordanians (0.015) (9). In line with a previous report that suggested ICAM1469*E is associated with inflammatory disease (22), our study shows that the frequency of ICAM1469*E is higher in Korean BD patients than in controls. We cannot draw any conclusion on the association of ICAM1G241R with BD, as described in Italian patients, because there was no case with ICAM1-G241R among the Korean BD patients in this study. ICAM1 mutations, especially ICAM1469*E, might act as another genetic susceptibility factor for BD in the Korean population as well as the recently described MICA A6 allele and HLA-B51 (23).

ACKNOWLEDGMENT

This study was supported by a grant (01-G05-08-001-00) from KISTEP, Korea.

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