Double-Positive Behçet Uveitis

Human Leukocyte Antigen B27 and B51

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**Objectives:** To describe the clinical characteristics of human leukocyte antigen (HLA) B27 and B51 double-positive Behçet uveitis and to determine whether the co-existence of HLA-B27 can affect Behçet uveitis.

**Methods:** We retrospectively reviewed the medical records of patients with Behçet uveitis and patients with HLA-B27-assOCIated non-Behçet uveitis who underwent HLA-B27 and HLA-B51 typing and were followed up for more than 3 years. We divided the patients into 3 groups according to HLA-B27/B51 status and compared the clinical outcomes. Main outcome measures were demographic features, uveitis characteristics, complications, treatments, and visual prognosis.

**Results:** Fourteen patients with HLA-B27(+)/B51(+) Behçet uveitis, 43 patients with HLA-B27(-)/B51(+) Behçet uveitis, and 41 patients with HLA-B27(+)/B51(−) non-Behçet uveitis were identified. HLA-B27(+)/B51(+) Behçet uveitis showed the demographic features similar to HLA-B27(−) counterparts. However, HLA-B27(+)/B51(−) Behçet uveitis showed less involvement of posterior segments, a less chronic course, fewer complications in posterior segments, and less use of systemic medication or surgical intervention for inflammatory control, similar to HLA-B27(+)B51(−) non-Behçet uveitis. The long-term vision prognosis of HLA-B27(+)/B51(+) Behçet uveitis was more favorable than that of HLA-B27(−)/B51(+) Behçet uveitis.

**Conclusions:** Our results indicate that HLA-B27(+) B51(−) Behçet uveitis is a benign subgroup of Behçet uveitis. The positivity of HLA-B27 may be a good prognostic factor in Behçet uveitis.

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**CLASS I HUMAN LEUKOCYTE antigen (HLA) is closely associated with disease susceptibility in patients with uveitis.** HLA-B51 is the primary gene involved in the pathogenesis of Behçet disease that can aid the diagnosis. Behçet uveitis usually shows a chronic course of relapsing uveitis affecting posterior segments during follow-up. However, about 10% of patients with Behçet uveitis develop intraocular inflammation limited to anterior segments. Classifying uveitis according to anatomical location and clinical course are important because of therapeutic strategy and vision prognosis.

HLA-B27 is the representative gene related to acute anterior uveitis with or without systemic diseases. HLA-B27-associated uveitis and Behçet uveitis are the most common causes of hypopyon uveitis from noninfectious origins. However, the overall clinical course and long-term vision prognosis are much different between Behçet uveitis and HLA-B27-associated uveitis. Although male sex and clinical severity of uveitis have been reported to be associated with the poor vision prognosis of Behçet uveitis, there is little evidence regarding the clinical significance of HLA-B27 positivity in Behçet uveitis.

In this study, we retrospectively analyzed the demographic features, uveitis characteristics, ocular complications, treatments, and long-term vision prognosis of HLA-B27 and HLA-B51 double-positive Behçet uveitis and compared the outcomes with other 2 groups, such as HLA-B27(−)/B51(+) Behçet uveitis and HLA-B27(+)/B51(−) non-Behçet uveitis.

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**METHODS**

We retrospectively reviewed the medical records of patients with Behçet uveitis and patients with HLA-B27-associated non-Behçet uveitis who were seen at the uveitis clinic at Chonnam National University Hospital (Gwangju, Korea) between 2000 and 2004. Informed consent was obtained for each patient who was tested for HLA typing of B27 and B51. Data collection was approved by our institutional review board. The patients with Behçet uveitis fulfilled the criteria of Behçet disease ac-
and retinal detachment. Initial visual acuity was defined as acuity obtained at the initial visit. Because visual acuity is usually severely affected during inflammatory episodes, we defined the final visual acuity as the visual acuity during remission at the last follow-up. The distribution of counts was analyzed using a Fisher exact test, correcting for multiple comparisons by requiring a $P$ value less than .05 on individual tests for a net confidence greater than 95%. Parametric data were compared using a Mann-Whitney $U$ test.

A total of 57 patients with $HLA-B27$–positive Behçet uveitis and 41 patients with $HLAB27$–associated non-Behçet uveitis were recruited in this study. All patients were Korean. Fourteen of 57 patients with $HLAB27$–positive Behçet uveitis concomitantly were $HLAB27$–positive. Recurrent oral ulcerations and skin involvements were confirmed by our rheumatologist in all the patients with $HLAB27$–positive Behçet uveitis, which manifested as recurrent genital ulcerations in 46 patients (81%) and positive pathergy test results in 23 patients (40%). There were no differences regarding systemic manifestations according to the presence of $HLAB27$. In 5 patients who were $HLAB27$ positive, uveitis was the crucial criterion for diagnosing Behçet disease. Two of 14 patients with $HLAB27$–positive Behçet uveitis concomitantly had ankylosing spondylitis diagnosed by pelvis $x$-ray, but the systemic manifestations of 2 patients were closer to Behçet disease than to ankylosing spondylitis. No patients with $HLAB27$–positive Behçet uveitis showed systemic features related to Reiter syndrome, inflammatory bowel disease, or psoriasis. All patients associated with $HLAB27$ uveitis were $HLAB27$ negative. Of 41 patients with $HLAB27$–associated uveitis, 15 were diagnosed with ankylosing spondylitis, 4 patients had Reiter syndrome, and the others showed no definite systemic associations.

The male-female ratio of $HLAB27$–positive Behçet uveitis was 2.5:1. This ratio was similar to that of $HLAB27$–positive Behçet uveitis (2.9:1) but was lower than that of $HLAB27$–positive non-Behçet uveitis (2.1:1). The mean age at uveitis onset was similar between $HLAB27$–positive Behçet uveitis and $HLAB27$–negative Behçet uveitis (31.7 vs 31.2 years), but the mean age of Behçet uveitis was significantly younger than that of $HLAB27$–negative Behçet uveitis (39.6 years, $P = .04$). The demographic features are described in Table 1.

Table 2 outlines the uveitis characteristics of $HLAB27$–positive Behçet uveitis compared with those of $HLAB27$–negative Behçet uveitis.
HLA-B27(−) B51(+) Behçet uveitis and HLA-B27(+) B51(−) non-Behçet uveitis at the initial visit or during follow-up. There were significant differences between HLA-B27(+) B51(+) Behçet uveitis and HLA-B27(−) B51(+) Behçet uveitis with respect to anatomical locations, clinical course, and ocular findings. Compared with HLA-B27(−) B51(−) Behçet uveitis, more involvement with anterior segments (P < .01), a more acute course (P < .02), and fewer sight-threatening conditions (P < .01) were observed in HLA-B27(+) B51(+) Behçet uveitis. These uveitis characteristics of HLA-B27(+) B51(+) Behçet uveitis were similar to those of HLA-B27(+) B51(−) non-Behçet uveitis. There were no differences between the groups regarding bilaterality and occurrence rates of hypopyon and papillitis. Two patients who concomitantly had Behçet disease and ankylosing spondylitis did not show the same uveitis characteristics. Bilateral panuveitis with retinal vasculitis was observed in a 23-year-old man, and unilateral recurrent anterior uveitis developed in a 36-year-old man.

**Table 3** lists the ocular complications of anterior and posterior segments at the initial visit or during follow-up. There were no statistically significant differences between groups in ocular complication rates. However, frequencies of visually significant cataract were lower in HLA-B27(+) B51(+) Behçet uveitis than in HLA-B27(−) B51(+) Behçet uveitis irrespective of the similar frequencies of glaucoma and posterior synechiae. Also, occurrences of macular edema, optic atrophy, and retinal new vessels were lower in HLA-B27(−) B51(+) Behçet uveitis than in HLA-B27(−) B51(−) non-Behçet uveitis. Accordingly, the numbers of patients who had received periocular steroids, systemic steroids, or immunosuppressive agents were significantly higher in HLA-B27(−) B51(+) Behçet uveitis than in HLA-B27(−) B51(−) Behçet uveitis (P < .01) (Table 4). The rates of surgical management by pars plana vitrectomy were significantly more frequent in HLA-B27(−) B51(+) Behçet uveitis than in HLA-B27(−) B51(−) Behçet uveitis (P = .03).

**Table 5** lists the long-term vision prognosis in this study. As expected from the results described earlier, more...
Our study demonstrates that HLA-B27(+)B51(+) Behçet uveitis, a subgroup of Behçet uveitis, is a specific disease entity characterized by a benign clinical course and favorable vision outcomes in comparison with HLA-B27(−)B51(+) Behçet uveitis and that clinical features of the HLA-B27(+)B51(+) Behçet uveitis are similar to those of HLA-B27(+)B51(−) non-Behçet uveitis. We found that demographic features of HLA-B27(+)B51(+) Behçet uveitis were closer to those of HLA-B27(−)B51(+) Behçet uveitis. In contrast, uveitis characteristics, ocular complications, treatment choices, and long-term vision outcomes of HLA-B27(+)B51(+) Behçet uveitis were closer to those of HLA-B27(+)B51(−) non-Behçet uveitis. Our study suggests that the presence of HLA-B27 in HLA-B51-positive Behçet uveitis may be a good prognostic factor.

Both HLA-B27 and HLA-B51 are known to be representative genes related to the specific syndrome of uveitis. There was laboratory evidence regarding the immunopathogenic roles of 2 genes in disease induction.11,12 Because the positivity of HLA-B51 showed a lot of the geographic variation, the status of HLA-B51 is not currently included in the diagnostic criteria for Behçet disease according to international criteria.13 However, many genetic studies indicated that a gene near HLA-B51 may play a role in the immunopathogenesis of Behçet disease.1,14,15 Furthermore, the diagnostic specificity of HLA-B51 positivity in Korean Behçet disease was 83% superior to that of recurrent oral ulceration and skin involvement even though the diagnostic sensitivity of HLA-B51 positivity was low (50%).15 Therefore, the positivity of HLA-B51 may be a separate finding that helps diagnose or classify Behçet disease. However, recent clinical studies indicated that HLA-B51 status of Behçet uveitis was not correlated with the disease severity.8,16

Table 4. Medical and Surgical Management of Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HLA-B27(−)B51(+) Behçet Uveitis (n=43)</th>
<th>P Value</th>
<th>HLA-B27(+)B51(+) Behçet Uveitis (n=14)</th>
<th>P Value</th>
<th>HLA-B27(+)B51(−) Non-Behçet Uveitis (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical steroid</td>
<td>34 (79.1)</td>
<td>.10</td>
<td>14 (100)</td>
<td>NA</td>
<td>41 (100)</td>
</tr>
<tr>
<td>Periocular steroid</td>
<td>38 (88.3)</td>
<td>&lt;.01a</td>
<td>6 (42.8)</td>
<td>.20</td>
<td>25 (60.9)</td>
</tr>
<tr>
<td>Systemic steroid</td>
<td>40 (93.0)</td>
<td>&lt;.01a</td>
<td>3 (21.4)</td>
<td>&gt;.99</td>
<td>9 (21.9)</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>39 (90.6)</td>
<td>&lt;.01a</td>
<td>3 (21.4)</td>
<td>&gt;.99</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>36 (83.7)</td>
<td>.31</td>
<td>10 (71.4)</td>
<td>&lt;.01a</td>
<td>0</td>
</tr>
<tr>
<td>Surgery, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract extraction</td>
<td>22 (51.2)</td>
<td>.07</td>
<td>3 (21.4)</td>
<td>&gt;.99</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Filtering procedure</td>
<td>11 (25.6)</td>
<td>.48</td>
<td>2 (14.4)</td>
<td>&gt;.99</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Pars plana vitrectomy</td>
<td>13 (30.2)</td>
<td>.03a</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.  
* Difference was significant.

Table 5. Vision Outcomes

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>HLA-B27(−)B51(+) Behçet Uveitis (n=3)</th>
<th>P Value</th>
<th>HLA-B27(+)B51(+) Behçet Uveitis (n=14)</th>
<th>P Value</th>
<th>HLA-B27(+)B51(−) Non-Behçet Uveitis (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20/40</td>
<td>6 (70.0)</td>
<td>&lt;.01a</td>
<td>6 (42.8)</td>
<td>.29</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>≥20/200</td>
<td>17 (39.5)</td>
<td>&lt;.01a</td>
<td>12 (85.6)</td>
<td>&gt;.99</td>
<td>34 (82.9)</td>
</tr>
<tr>
<td>&lt;20/200</td>
<td>26 (60.5)</td>
<td>NA</td>
<td>2 (14.4)</td>
<td>NA</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Final follow-up, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20/40</td>
<td>3 (4.7)</td>
<td>&lt;.01a</td>
<td>3 (78.4)</td>
<td>.71</td>
<td>33 (80.5)</td>
</tr>
<tr>
<td>≥20/200</td>
<td>32 (74.4)</td>
<td>.26</td>
<td>13 (92.8)</td>
<td>&gt;.99</td>
<td>38 (92.7)</td>
</tr>
<tr>
<td>&lt;20/200</td>
<td>11 (25.6)</td>
<td>NA</td>
<td>1 (7.2)</td>
<td>NA</td>
<td>3 (7.3)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.  
* Difference was significant.

patients with HLA-B27(+)-B51(+) Behçet uveitis had an initial visual acuity of more than 20/40 or 20/200 than did patients with HLA-B27(−)-B51(+) Behçet uveitis (P < .01). The risk of decrease in visual acuity to less than 20/40 (driving vision) during follow-up was significantly lower in HLA-B27(+)-B51(+) Behçet uveitis than in HLA-B27(−)-B51(+) Behçet uveitis (21.6% vs 95.3%, P < .01). The risk of decrease in visual acuity to less than 20/200 (legal blindness) was also lower in HLA-B27(+)B51(+) Behçet uveitis than in HLA-B27(−)-B51(+) Behçet uveitis (7.2% vs 25.6%), although this difference was not statistically significant (P = .26). Vision outcomes of HLA-B27(+)-B51(+) Behçet uveitis were comparable with those of HLA-B27(+)-B51(−) non-Behçet uveitis.
sults imply that HLA-B27 status in HLA-B51–positive Behçet uveitis may be correlated with disease severity at the initial visit or during follow-up. Currently, we do not know the function of HLA-B27 on the disease progression or posterior-segment involvement of Behçet uveitis. However, a possible explanation is that HLA-B27 may act as the dominant gene against HLA-B51 in Behçet uveitis.

Male sex and early age at uveitis onset have been reported to be poor prognostic factors in Behçet uveitis. Our data regarding these demographic factors of all the patients included were consistent with previous reports. Because the male-female ratio and mean age at uveitis onset were similar between HLA-B27 (+) B51 (+) Behçet uveitis and HLA-B27 (−) B51 (+) Behçet uveitis, the demographic factors do not affect our results. In addition, in accordance with previous reports, we found that the male predominance and younger age at uveitis onset were noted in Behçet uveitis compared with HLA-B27–associated non-Behçet uveitis.

The uveitis characteristics of HLA-B27 (−) B51 (+) Behçet uveitis in our study are similar to other studies in different ethnic populations. In contrast, HLA-B27–associated uveitis shows less involvement of posterior segments and a more benign clinical course, similar to our patients. These differences in clinical findings may be attributed to the different immune effectors and cytokine environments. Interestingly, we observed that the clinical characteristics of HLA-B27 (+) B51 (+) Behçet uveitis included acute or recurrent anterior uveitis with less posterior-segment involvement. Furthermore, in some samples from our previous reports, we found that the ocular infiltrating immune cells and intraocular cytokines were similar between HLA-B27 (+) B51 (+) Behçet uveitis and HLA-B27 (+) B51 (−) non-Behçet uveitis (data not shown). Therefore, the clinical features of HLA-B27 (+) B51 (+) Behçet uveitis are close to those of HLA-B27 (+) B51 (−) non-Behçet uveitis.

All ocular complications were observed less frequently in HLA-B27 (+) B51 (+) Behçet uveitis compared with HLA-B27 (−) B51 (+) Behçet uveitis. These findings were more prominent in the posterior segments that did directly affect vision outcomes. Because the uveitis characteristics and ocular complications of HLA-B27 (+) B51 (+) Behçet uveitis were the same as those of HLA-B27 (−) B51 (−) non-Behçet uveitis, there was much less frequent use of systemic steroids or immunosuppressive agents for control of intraocular inflammation. Our previous report suggested that vitreectomy in persistent Behçet uveitis, despite aggressive treatment with medication, might be helpful in controlling inflammation. However, in this study, no patients with HLA-B27 (+) B51 (+) Behçet uveitis needed to receive vitrectomy for control of intraocular inflammation. These differences indicate, with aggressive medical or surgical treatments as proxy measures of severity, that patients with HLA-B27 (−) B51 (+) Behçet uveitis clearly suffer more severe treatment-resistant uveitis than do patients with HLA-B27 (+) B51 (−) Behçet uveitis.

Overall vision outcomes in this study are in agreement with previous studies. Our patients with HLA-B27 (+) B51 (+) Behçet uveitis appear to have favorable long-term vision prognosis. The risks of a decrease in visual acuity over 3 years to less than 20/200, or to less than 20/40 in particular, are much lower in HLA-B27 (+) B51 (+) Behçet uveitis than in HLA-B27 (−) B51 (+) Behçet uveitis. These findings support the idea that HLA-B27 (+) B51 (+) Behçet uveitis is a mild form of Behçet uveitis.

One may argue that patients with HLA-B27 (+) B51 (+) Behçet uveitis could be classified into HLA-B27–associated uveitis rather than Behçet uveitis according to the uveitis characteristics of our results. However, it is reasonable to classify HLA-B27 (+) B51 (+) Behçet uveitis as a subgroup of Behçet uveitis. First, the systemic manifestations of HLA-B27 (+) B51 (+) Behçet uveitis are not attributed to HLA-B27–associated systemic diseases but to Behçet disease. Second, the positivity of HLA-B51 may be a genetic marker for Behçet disease. Third, only 2 patients with HLA-B27 (+) B51 (+) Behçet uveitis concurrently had ankylosing spondylitis, and the uveitis characteristics of 1 patient are closer to Behçet uveitis than to HLA-B27–associated uveitis.

In conclusion, HLA-B27 (+) B51 (+) Behçet uveitis is a benign subgroup of Behçet uveitis, and the clinical characteristics resemble HLA-B27–associated non-Behçet uveitis. Therefore, the presence of HLA-B27 in Behçet uveitis may be a good prognostic factor.

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Financial Disclosure: None reported.

REFERENCES


**Silicone Oil Maculopathy**

Daniel M. Gore, BSc, MBBS; Romesh I. Angunawela, MD, MRCOphth; Riaz Asaria, MD, BM, FRCOphth

Fundus photograph with magnified insert showing numerous glistening subretinal silicone oil droplets of varying sizes at the macula. Six months previously, the patient had undergone surgery for diabetic tractional retinal detachment including vitrectomy and retinal tamponade with silicone oil.