Letters

Possession of the HLA-DRB1*1501 Allele and Visual Outcome in Idiopathic Intermediate Uveitis

Idiopathic intermediate uveitis (IIU) is a potentially sight-threatening inflammatory disease characterized by breakdown of the blood-retina barrier with consequent leukocytic infiltration of the vitreous and retina. Poor visual outcome has been associated with cystoid macular edema, poor vision at presentation, and male sex. The human leukocyte antigen (HLA) allele DRB1*1501 has long been associated with multiple sclerosis (MS). Tang et al prospectively analyzed 18 patients and found that HLA-DRB1*1501 conferred increased risk of developing IIU associated with MS in some patients.

The purposes of this study were to prospectively evaluate the association between the HLA-DRB1*1501 allele and IIU in patients and to determine whether HLA-DRB1*1501 might be a separate independent risk factor for visual loss.

Methods | Participants included 85 patients with IIU and 300 healthy, demographically matched controls. Idiopathic intermediate uveitis was classified on the basis of ophthalmological examination and fluorescein angiography findings. Patients with systemic inflammatory, neoplastic, or infectious diseases were excluded, as were patients with a history of optic neuritis. Written informed consent for HLA typing was obtained from all individuals. This study received approval from the St Thomas’ Ethical Committee and adheres to the Declaration of Helsinki.

Patients were reviewed at 3 months, 5 years, and 10 years (where possible) between 2000 and 2014. Additional appointments were given as required to adequately maintain control of intraocular inflammation.

Visual acuity (VA) of 6/12 or better was defined as a good outcome. Genomic DNA was extracted and genotyped for the HLA class II allele HLA-DRB1*1501 using polymerase chain reaction amplification with sequence-specific primers. Polymerase chain reaction products were electrophoresed and read using ethidium bromide and UV illumination.

Results | The Table shows VA and demographic data. Thirty-eight cases (45%) were HLA-DRB1*1501 positive compared with 90 controls (30%) (15% difference; $\chi^2 = 6.45; P = .007$; odds ratio = 1.89; 95% CI, 1.15-3.09).

We found no association between VA and possession of the HLA-DRB1*1501 allele. Twelve HLA-DRB1*1501-positive patients (31%) had a VA less than 6/12 at the end of the study, compared with 8 HLA-DRB1*1501-negative patients (17%) (14% difference; $P = .15$; relative risk = 1.52; 95% CI, 0.94-2.47). There was no identifiable difference in sex between HLA-DRB1*1501-positive and HLA-DRB1*1501-negative patients (2.5% difference; $P = .65$; odds ratio = 0.77; 95% CI, 0.31-1.91). The mean (SD) age at presentation was 62.09 (11.6) years for the HLA-DRB1*1501-positive patients and 59.72 (16.04) years for the HLA-DRB1*1501-negative patients ($P = .46$).

Discussion | Our findings are in agreement with the previously reported association between IIU and HLA-DRB1*1501. However, we were unable to identify any association between possession of the HLA-DRB1*1501 allele and sex or age at presentation, as has been found in MS. We also did not find an association between HLA-DRB1*1501 and final VA.

Our exclusion criteria, prospective design, and extended follow-up distinguish this study from those previously reported. The patient population was comparable to those in other studies in terms of race, sex, and age.

The results reflect the relatively benign nature of IIU in that 76% of our patients had good vision at 10 years. Similarly, Raja et al reported a VA higher than 6/12 in 82% of their patients after 4 years.

The prediction of visual outcome from haplotype analysis has not been supported by this study. However, our findings cannot rule out the possibility that IIU is made up of a number of separate disease processes, of which some affect all age groups and others (HLA-DRB1*1501 related) represent a forme fruste of MS. It is possible that patients in this study developed an associated systemic disease after their second review at 5 years but were not seen again at 10 years.

Finally, our data suggest that VA at 3 months reliably predicts vision at 5 and 10 years. This is important for future

Table. Patient Demographic Characteristics and Visual Acuity During the Study Perioda

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Follow-up, No. (%)</th>
<th>3 mo (n = 85)</th>
<th>5 y (n = 85)</th>
<th>10 y (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (36)</td>
<td>31 (36)</td>
<td>8 (24)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>54 (64)</td>
<td>54 (64)</td>
<td>26 (76)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83 (98)</td>
<td>83 (98)</td>
<td>32 (94)</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6/12</td>
<td>73 (85)</td>
<td>67 (79)</td>
<td>26 (76)</td>
<td></td>
</tr>
<tr>
<td>&lt;6/12</td>
<td>12 (15)</td>
<td>18 (21)</td>
<td>8 (24)</td>
<td></td>
</tr>
</tbody>
</table>

* The mean age at presentation was 40 years (range, 14-74 years).
clinical studies as a shorter follow-up time can be used to determine clinical efficacy.

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Author Contributions: Dr Wallace had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stanford, Wallace.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Petrushkin, Thomas, Stanford, Wallace.

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Statistical analysis: Petrushkin, Thomas.

Administrative, technical, or material support: Petrushkin, Kondeatis.

Study supervision: Vaughan, Stanford, Edelsten, Wallace.

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OBSERVATION

A Case of Bilateral, Multiple, Symmetric, Concentric Ring-Shaped Opacities in the Cornea

This case report describes a rare and intriguing case of bilateral concentric ring-shaped opacities not associated with any ocular or systemic conditions.

Report of a Case | A man in his 70s with no specific ocular symptoms presented for a routine ophthalmic examination. He had no history of eye surgery. Best spectacle-corrected visual acuity was 20/20 OU. Results of slit-lamp examination of the right eye showed a normal conjunctiva with healthy ocular adnexa. The cornea showed a normal luster and even surface with no distinct arcus senilis. While the anterior stroma was normal, 4 symmetric concentric ring-shaped opacities were seen in the posterior corneal stroma (Figure, C). All the rings were complete, with the outermost (first) ring located approximately 4 mm from the limbus. From the periphery to the center, the approximate vertical diameters of the 4 rings were 6.0 mm, 4.8 mm, 4.5 mm, and 3.6 mm, respectively (Figure, D and E).

The rings were alternatively distinct, with the outermost and third rings more sharply demarcated (Figure, A and B). The surface on the rings was smooth and did not show any obvious deposits, pigmentation, or serratations. The peripheral cornea showed a posterior crocodile shagreen. Results of the rest of the anterior segment and posterior segment examination were normal, except for mild nuclear sclerosis of the crystalline lens. Examination of the left eye showed similar findings to those in the right eye. The corneal presentation of the left eye was identical to that of the right eye. In addition, there was a small nasal pterygium in the left eye. Keratometry readings were 43.4 × 43.4 diopters (D) OD and 43.0 × 44.8 D OS. Corneal sensations were normal in both eyes. Laser scanning in vivo confocal microscopy (HRT [Heidelberg Retina Tomograph] II with RCM [Rostock Cornea Module]; Heidelberg Engineering GmbH) of the right eye done at the level of the lesions revealed long bandlike structures with thin streaks of white lines interspersed (Figure, F). No cellular infiltration was seen. The confocal images were similar in the cornea of the left eye.

Results of the patient's annual physical examination did not reveal any abnormalities. Specifically, the patient's lipid and glucose levels were within the normal range. Based on the corneal findings, the patient was subjected to additional systemic investigations that included measurement of serum copper and iron levels to rule out metallic deposits, both of which were found to be normal. Subsequently, his adult children were also screened and did not have corneal opacities.

Discussion | Deposits in the cornea have been described in all corneal layers. These lesions are either pigmented or nonpigmented and may take the shape of rings, lines, and amorphous deposits. 1-3 Our patient presented with symmetric bilateral concentric ring-shaped opacities in the cornea with clear intervening stroma.

Bilateral, single, ring-shaped corneal opacities have been previously described. Melles et al 4 reported that Asher described bilateral gray-white rings in the midperipheral cornea in a young patient with recurrent iritis of unknown cause. Melles et al 5 subsequently described bilateral midperipheral anterior stromal ring-shaped corneal opacities in a young healthy individual and postulated that these may be a rare corneal dystrophy or micro deposits of unknown origin. In a series of 2 cases, Bronn 6 described similar bilateral corneal rings (one corneal ring in both eyes of both patients) associ-