

Lack of the HLA-DR2 specificity in multifocal choroiditis and panuveitis

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Abstract

The prevalence of the HLA-B7 and HLA-DR2 specificities in 17 unrelated patients with multifocal choroiditis and panuveitis, 11 with and six without subretinal neovascularisation, was evaluated and compared with those of two different groups. The first group was 17 patients with subretinal neovascularisation associated with presumed ocular histoplasmosis syndrome, and the second was a group of 105 eye patients with no retinal disease. HLA-DR2 was not found in any patient with multifocal choroiditis and panuveitis, but it was found in 13 patients with presumed ocular histoplasmosis syndrome ($p=6.72 \times 10^{-5}$, comparison of the groups with subretinal neovascularisation). The lack of HLA-DR2 was also significant in comparison with the control group of eye patients ($p=0.041$). This study suggests that patients with multifocal choroiditis and panuveitis and presumed ocular histoplasmosis syndrome have differing genetic predispositions, though the fundus pictures in these entities have many similarities.

Multifocal choroiditis and panuveitis,¹ like presumed ocular histoplasmosis syndrome, causes multiple focal sharply circumscribed areas of choroidal atrophy and is associated with subretinal neovascularisation. Unlike presumed ocular histoplasmosis syndrome (POHS), patients with multifocal choroiditis and panuveitis (MCP) have inflammation of the anterior chamber and vitreous. In addition patients with MCP are more likely to be young myopic women, to have recurrent crops of new atrophic chorioretinal lesions,² and most to have negative reactions to *Histoplasma capsulatum* tests.¹

Peripheral atrophic scarring in POHS has been associated with an increased prevalence of the HLA-DR2 antigen.³ Subretinal neovascularisation in POHS has been associated with an increased prevalence of the HLA-B7 and HLA-DR2 antigens.^{3,4} We tested 17 patients with multifocal choroiditis and panuveitis to determine possible HLA-B7 and HLA-DR2 associations.

Patients and methods

The patients were examined at the Manhattan Eye, Ear, and Throat Hospital or referred to the private practice of one of the investigators from 1983 until the present time as a part of a larger study of subretinal neovascularisation. Presumed ocular histoplasmosis syndrome was diagnosed in patients when there were atrophic chorio-

retinal spots, no intraocular inflammation, and when the histoplasmin skin test was positive (histoplasmin antigen, Parke-Davis, standardised to US Reference Standard, Lot H-42 (1:100), US Public Health Service, National Center for Disease Control). Multifocal choroiditis and panuveitis was diagnosed if the patient had atrophic chorioretinal spots and recurrent bouts of anterior chamber or vitreal inflammation. Histoplasmosis complement fixation titres were tested on seven patients (New York State Department of Health Mycologic Serology Laboratory), and eight of the MCP patients had histoplasmin skin tests. All histoplasmosis tests were negative in the patients with MCP. The group of control eye patients were obtained from the Manhattan Eye, Ear, and Throat Hospital and from the private practice of one of the investigators, and none of these patients had a history of uveitis or retinal disease.

Blood was drawn from the patients, and the standard National Institutes of Health (NIH) lymphocytotoxicity assay was employed for HLA typing for B7 and DR2 (performed by



Figure 1A



Figure 1B

Figure 1: Comparative photographs showing two patients with atrophic chorioretinal spots and disciform scarring. A: Presumed ocular histoplasmosis syndrome. B: Multifocal choroiditis and panuveitis. Patient A had a positive histoplasmin skin test. Patient B had a negative histoplasmin skin test and a recurrent intraocular inflammation.

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Rogosin Institute, Laboratory of Immunogenetics and Transplantation, New York, New York). Cases and controls signed an informed consent for participation in this study. The consent and study design were approved by the Institutional Review Board of Manhattan Eye, Ear, and Throat Hospital.

Categorical data were analysed by the 2-tailed Fisher's exact test,⁵ and a p value of 0.05 or less was considered significant.

Results

The average age of the 17 MCP patients was 34.2 years (SD 15.5 years); 15 were females, 10 were myopic. Two patients had unilateral disease, and one of these had myopia only in the affected eye. All patients had a history of vitritis, and nine had a history of anterior uveitis.

No patient with MCP had HLA-DR2, while 13 of the 17 patients (76%) with POHS and subretinal neovascularisation had HLA-DR2. In an attempt to compare similar patients we compared the 11 patients with MCP and subretinal neovascularisation with the 17 patients with POHS and subretinal neovascularisation. The prevalence of HLA-DR2 was significantly greater in the POHS group ($p=6.72 \times 10^{-5}$).

HLA-DR2 was found in 20% of the 105 eye patients used as a control, a frequency that is significantly greater than in patients with MCP ($p=0.041$). HLA-B7 was found in two patients with MCP (11.8%), which was less than in patients with presumed ocular histoplasmosis (8 of 17, 47%) but this difference did not reach statistical significance ($p=0.057$). Sixteen of the group of 105 eye patients used as a control had HLA-B7 (15.2%), which was not significantly different from that in patients with MCP ($p=0.995$).

Discussion

In our patient group and in other studies^{3,4} HLA-B7 shows a weaker association with POHS than does HLA-DR2. The prevalence of HLA-B7 in patients with multifocal choroiditis and panuveitis was less than the POHS group, but the p value did not reach statistical significance ($p=0.057$). The numbers of MCP and POHS patients are admittedly small, because multifocal choroiditis and panuveitis is an uncommon disease, and the New York area is not endemic for histoplasmosis. Previous studies have linked HLA-B7 with POHS, but they did not evaluate the effects of the strong linkage

disequilibrium between HLA-B7 and HLA-DR2⁶ and the confounding introduced by this linkage disequilibrium. HLA-DR2 shows a strong association with POHS, and it is possible that HLA-B7 seems to show a correlation with POHS because of the linkage disequilibrium between HLA-DR2 and HLA-B7.

In our group of patients and in another study HLA-DR2 showed a strong association with subretinal neovascularisation in POHS, suggesting that the presence of HLA-DR2 is a risk factor for the development of POHS. Conversely, no patient with multifocal choroiditis and panuveitis had HLA-DR2. (Although the best point estimate for the true prevalence of HLA-DR2 in the patients is zero, the 95% confidence interval extends from 0 to 0.185).⁷ The striking differences in the expression of HLA-DR2 between these two groups suggests that the patients have different genetic predispositions even though the predominant ocular findings in both are atrophic spots and subretinal neovascularisation. This finding may be useful clinically in helping make the diagnosis of MCP. There was a less striking but statistically significant decrease in the prevalence of HLA-DR2 in MCP as compared with the 105 control patients. No aetiological agent has been isolated in MCP, but in one study all 10 patients with MCP had positive IgM or Epstein-Barr early antigen antibody titres while showing signs of being previously exposed to the virus (elevated IgG viral capsid antigen antibody titres).⁸ Multifocal choroiditis and panuveitis might be caused by the Epstein-Barr virus or a yet unidentified factor in people with certain risk factors, that is, those with female sex, myopia, and a decreased prevalence of HLA-DR2.

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