
An immunological basis for neurological involvement in Vogt-Koyanagi-Harada syndrome was sought by means of the migration-inhibition factor technique with human myelin basic protein. The test was carried out in four patients who had recent manifestations of the syndrome, two of whom were evaluated both before and after initiation of steroid treatment; in one patient 4 years after recovery from the syndrome; in three patients having uveitis of other causes; and in 12 healthy controls. The results were positive in all four patients who had recent manifestations, whereas they were negative in all the others. This finding may constitute evidence of a cell-mediated immunity toward components of the nervous system in this disease entity.

The Vogt-Koyanagi-Harada (VKH) syndrome is a uveal and meningeal inflammation variably associated with encephalitis, cranial nerve involvement (mainly of nerves II and VIII), and hair and skin changes (poliosis, canities, alopecia, and vitiligo). The uveitis may be granulomatous or non-granulomatous. Viral infection, endocrine disturbances, autoimmunity, or a combination of these have been suggested factors in the pathogenesis of this entity, but the etiology is still unclear. The multisystemic involvement may be due to immunological reactivity toward a common, shared tissue antigen and to diffuse autoantigenicity. Cell-mediated immunity (CMI) toward uveal antigen has been demonstrated in both VKH and sympathetic ophthalmitis.

 Immunity to myelin basic protein has been implicated in the pathophysiology of a number of inflammations involving the central nervous system (CNS) that occur in both experimental animals and humans. Reactivity to human myelin basic protein (HBP) has been demonstrated in retrolubular neuritis, occurring either in an isolated form or associated with multiple sclerosis, and it may play a major role in the development of this disease.

Since patients with VKH uveomeningitis present involvement of both ocular and CNS structures, we undertook a study to determine whether or not there is CMI toward HBP in these patients.

Materials and methods

Subjects. The subjects comprised the following four groups: (1) four patients who had recent exudative detachments, bilateral uveitis, pathological electro-oculograms (EOGs), and increased cellular content in the spinal fluid, respectively (in two of these patients, analysis was performed both before and after the initiation of steroid treatment; (2) one patient evaluated 4 years after recovery from VKH syndrome; (3) three patients with recent posterior uveitis other than VKH (two of unknown etiology, one with toxoplasmosis) who had not been treated with a steroid regimen before the MIF test was performed; and (4) 12 healthy controls.

Antigens. HBP was extracted from the myelin of human brain. A concentration of 10 µg/ml of medium, which did not affect the normal migration of macrophages, was selected as the optimal dose of antigen in the macrophage-migration test.

Lymphocytes, macrophages, and macrophage migration-inhibition factor (MIF) test. The preparation of the subjects' lymphocytes and of the guinea pig macrophages and performance of the MIF test were carried out as described in a previous paper. A migration index of 0.80 or less was considered significant for macrophage migration inhibition.

Results. The results of the MIF tests are presented in Table I. In all four patients who had recently had VKH syndrome, the MIF tests were positive to HBP. When the test was repeated 1 month after initiation of steroid treatment, this result was negative in Patients 1 and 2. In Patient 1, the MIF test to HBP was again positive when it

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Migration index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recent VKH prior to steroid treatment</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>1 month after initiation of steroids</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>6 months after onset of VKH and</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>1 month after withdrawal of steroids</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Recent VKH prior to steroid treatment</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>1 month after initiation of steroids</td>
<td>0.82</td>
</tr>
<tr>
<td>3</td>
<td>Recent VKH</td>
<td>0.65</td>
</tr>
<tr>
<td>4</td>
<td>Recent VKH</td>
<td>0.57</td>
</tr>
<tr>
<td>5</td>
<td>4 years after VKH</td>
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</tr>
<tr>
<td>6</td>
<td>Uveitis of other cause</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>Uveitis of other cause</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>Uveitis of other cause</td>
<td>1.0</td>
</tr>
<tr>
<td>9-20</td>
<td>Healthy controls</td>
<td>1.83 ± 0.15</td>
</tr>
</tbody>
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Table I. MIF test in response to HBP antigen in patients with VKH syndrome or uveitis of other causes and in healthy controls

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was repeated 6 months after onset of the disease and 1 month after steroid treatment had been discontinued. In contrast, the MIF tests to HBP all were negative in the patient who had had VKH 4 years earlier, in the three patients with uveitis of other causes, and in the 12 healthy controls.

Discussion. Cell-mediated reactivity toward HBP was demonstrated in a small group of patients who had VKH syndrome. It was found that there was a positive reaction to HBP, as measured by MIF test, in all of the four cases of recent VKH syndrome. Negative results were obtained in two of these patients when they were tested again 1 month after corticosteroid administration and in one patient who had recovered from the disease 4 years earlier. Negative MIF results were also obtained in the three patients with other forms of uveitis and in the 12 normal controls.

In patients with recent onset of VKH disease, positive MIF test results were found despite the absence of any clinical neurological signs except pleocytosis of the cerebrospinal fluid. This observation seems to be consistent with the hypothesis that an in vivo hypersensitivity to HBP may play a role in the pathological process and that it could be one of the common denominators in this multisystemic disease. Alternatively, it is possible that reactivity toward HBP is a secondary phenomenon resulting from nonimmunologically mediated alterations of CNS tissues.

In their investigations of multiple sclerosis, Recklin et al.,29 Meyers,30 and Sheremata et al.31 found a correlation between the sensitization to HBP in vitro and acuteness of illness. In two of our cases, the MIF results were positive initially but were negative 1 month after administration of corticosteroid therapy; in one of these cases, the results were again found to be positive 1 month after withdrawal of treatment and during a recurrence.

Ohno et al.,34 showed that early systemic administration of corticosteroids may lessen the incidence of multisystemic involvement in VKH. It is possible that future investigations of specific in vitro CMI performed toward ocular tissues and HBP antigens will increase our understanding of the importance of immunological phenomena in patients who have VKH uveomeningecephalitis.

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Key words: Vogt-Koyanagi-Harada syndrome, cell-mediated immunity, migration inhibition factor, human myelin basic protein

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Chemotactic activity and cellular infiltration of aqueous humor in experimental herpes simplex uveitis. JANG O. OH AND MARCELA A. KOPAL.

The degree of chemotactic activity of the aqueous humor for a specific type of inflammatory cell is in direct proportion to the extent of such cells infiltrating the aqueous humor of rabbits with either primary or secondary experimental herpes simplex uveitis. Chemotaxis may thus be a contributing factor in the pathogenesis of herpetic uveitis.

Many infections, and sometimes the different stages of a single infection, are associated with specific inflammatory responses, each characterized by a predominance of one type or another of inflammatory cell. In herpes simplex uveitis in rabbits, primary uveitis has a predominantly polymorphonuclear cell (PMN) infiltration in the early phase and a mononuclear cell infiltration in the late phase. In secondary uveitis, on the other hand, the cellular response is largely mononuclear throughout the disease period. Unfortunately, we still have very little information about the factors that promote the infiltration of a particular type of cell at the site of the uveitis at a given time.

One useful approach to the study of various kinds of inflammatory cell responses is to investigate the factors that cause specific unidirectional migration (chemotaxis) of inflammatory cells. The data to be presented in this paper show that the aqueous humor exerts a chemotactic effect on PMNs and macrophages and that chemotaxis may be a contributing factor in the pathogenesis of herpetic uveitis.

Materials and methods. We used partially purified type 1 herpes simplex virus (HSV),2 Shealey strain, with an infectivity titer of $3.5 \times 10^5$ 50% tissue culture infectious doses (TCID$_{50}$) per milliliter. With this strain we produced primary herpes simplex uveitis in both eyes of New Zealand white male rabbits (2 kg body weight) by injecting 0.1 ml of a suspension containing $10^7$ TCID$_{50}$ of live HSV into the anterior chamber of each eye. Secondary uveitis was produced by anterior chamber injections of the same dose of virus in both eyes of...