Elevated Vitreous Concentration of Monoclonal Immunoglobulin Manifesting as Schlieren in Juvenile Rheumatoid Arthritis–Associated Uveitis

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We report the clinical findings and analysis of the immunoglobulin (Ig) composition of the vitreous of a 10-year-old girl with juvenile rheumatoid arthritis–associated uveitis. The vitreous had a schlieren appearance at the time of pars plana lensectomy and vitrectomy. Analysis of the vitreous fluid revealed marked elevation of IgG, IgM, IgA, and albumin levels relative to vitreous fluids from control patients without uveitis. The immunoglobulin coefficients were also elevated for the IgG and IgM classes of immunoglobulins. Immunofixation electrophoresis of the vitreous fluid revealed 2 distinct bands of restricted electrophoretic mobility. These studies suggest that there may be local (intraocular) production of immunoglobulins as an immunologic response in ocular inflammatory diseases such as juvenile rheumatoid arthritis–associated uveitis and that this immunologic response may be monoclonal (possibly biclonal or oligoclonal) in nature.

Schlieren, a phenomenon caused by the difference in refractive indices of 2 different media that mix together, is most commonly seen in vitreoretinal surgery when subretinal fluid, with its high protein content, passes through a retinal tear or hole and mixes with the infusion solution in the vitreous cavity. Monoclonal immunoglobulin (Ig) detected by direct immunofluorescent microscopy has been reported in the vitreous of patients with reticulum cell sarcoma masquerading as uveitis and exudative retinal detachment. Intraocular immunoglobulin production has been shown in patients with ocular toxoplasmosis and acute retinal necrosis syndrome. However, to the best of our knowledge, there is no published report of elevated vitreal concentration of immunoglobulin manifesting as schlieren in patients with uveitis of noninfectious or nonmalignant origin.

REPORT OF A CASE

A 10-year-old African American girl had pauciarticular juvenile rheumatoid arthritis (JRA), which was diagnosed at age 18 months and had been limited to the joints in her knees, and positive findings for antinuclear antibody. At age 5 years, the patient developed bilateral JRA-associated uveitis, which was subsequently stabilized when the patient was 9 years old.

At the initial examination in 1998 (age 10 years), the patient had noted gradual loss of vision in both eyes for 1 year. On examination, her best-corrected visual acuity was 8/200 OD and 2/200 OS. Intraocular pressure was 4 mm Hg bilaterally. Findings from slitlamp biomicroscopy revealed white and quiet conjunctivae and anterior chamber flare without keratic precipitates. There were 2+ flare without cells in the anterior chambers, bilateral 360° posterior synechiae, and dense, white cataracts, precluding views of the posterior segments. Findings from B-scan ultrasonography revealed a small, noncalcified, round, subretinal mass associated with a blind spot in the left eye. Ultrasound biomicroscopy revealed a vitreous mass associated with a small, subretinal, shaggy mass. There were 2+ vitreous cells with 2+ vitreous debris. The vitreous was not liquefied. The posterior segment was normal. The diagnosis was probable posterior subcapsular cataract, bilateral posterior subcapsular cataract, bilateral cataract, and bilateral vitritis.

Initially, the patient underwent pars plana lensectomy, vitrectomy, and pupil-lary synechiolysis in the left eye. Schlieren was noted in the vitreous during surgery, but vitreous samples were not obtained for immunological analysis. Subsequently, the
patient underwent similar surgical procedures in the right eye. At the time of the surgery, the vitreous again appeared liquefied and had a schlieren appearance. Vitreous and blood specimens were sent for pathologic analysis for immunoglobulin quantification and immunofixation electrophoresis (IFE).

Vitreous fluid (5 mL) from the patient with JRA-associated uveitis (patient 1) was concentrated using a molecular filtration device (Minicon B15 Spinal Fluid Concentrator; Amicon Inc, Beverly, Mass) to 500 µL and subjected to immunoglobulin quantification and IFE. Blood serum of the patient was studied in a similar fashion. Vitreous fluids from the 4 control patients (patients 2, 3, 4, and 5) were processed and analyzed by identical techniques. During the vitrectomy of each of the 5 patients, the in vivo vitreous was collected. Serum samples were available only from patient 5, who was a 73-year-old woman with diabetes mellitus who developed proliferative diabetic retinopathy and nonclearing vitreous hemorrhage. Patient 2 was an 81-year-old woman with vitritis, cystoid macular edema, and epiretinal membrane who underwent diagnostic vitrectomy to rule out lymphoma. Patient 3 was a 54-year-old woman, and patient 4 was a 62-year-old woman; both had full-thickness macular holes.

Serum protein electrophoresis was performed (REP Ultra SPE-30 [Ponceau S]; Helena Laboratories, Beaumont, Tex). Levels of the 3 immunoglobulin classes (IgG, IgA, and IgM) were measured using a nephelometer and reagents (Array; Beckman, Brea, Calif). Immunofixation electrophoresis was performed using an electrophoresis system and reagents (Paragon; Beckman, Fullerton, Calif).

The vitreous to serum immunoglobulin coefficients were calculated as follows:

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\begin{align*}
\text{Vitreous Immunoglobulins} & = \frac{\text{IgG (IgG, IgA, IgM)}}{\text{Vitreous Albumin}} \\
\text{Serum Immunoglobulins} & = \frac{\text{IgG, IgA, IgM}}{\text{Serum Albumin}}
\end{align*}
\]

The anticipated reference range of this coefficient based on human cerebral spinal fluid IgG index and experimental uveitis is 0.2 to 0.8.8,9 Immunofixation electrophoresis of the vitreous of patient 1 revealed 2 bands of restricted electrophoretic mobility in the IgG lane with corresponding bands in the kappa lane (Figure 1). Results of the serum IFE failed to detect any band of restricted electrophoretic mobility (Figure 2). The results of immunoglobulin quantification and IFE for patient 1 and control subjects (patients 2, 3, 4, and 5) are summarized in the Table.

The calculated immunoglobulin coefficients (vitreous to serum ratio) of patient 1 are as follows: 1.9 (IgG), 0.7 (IgA), and 2.1 (IgM). Blood serum was not available for patients 2, 3, and 4; therefore, immunoglobulin coefficients could not be calculated. In patient 5, the IgG coefficient is 0.7. Since vitreous concentration of IgA and IgM are too small to have specific values, the coefficients for these classes of immunoglobulins could not be calculated.

We have described a case of elevated intraocular concentration of albumin and monoclonal (possibly bicalon or oligoclonal) immunoglobulin in a child with JRA-associated uveitis, which manifested clinically as the appearance of schlieren in the vitreous. There was no retinal tear, hole, or detachment. Thus, the schlieren was not due to sequestered subretinal fluid egressing into the vitreous, but most likely was secondary to elevated concentrations of immunoglobulins and albumin in the vitreous. The presence of 2 distinct bands of restricted electrophoretic mobility on IFE corresponding to the IgG and kappa lanes indicates that there is specific amplification and accumulation of the clonal antibody, and it is unlikely to be artifactual. The immunoglobulin quantification of the vitreous from the patient with JRA also showed significant elevation of vitreal IgG relative to vitreal immunoglobulin levels of control patients. The value of the immunoglobulin coefficient between cerebral spinal fluid and serum for most immunoglobulins is normally between 0.2 and 0.8, as illustrated by the coefficient in patient 5. In patient 1, the coefficient for IgG is 1.9, more than a 2-fold increase compared with the upper normal value of 0.8; the coefficient for IgM was also elevated at 2.1.

The vitreous normally contains 0.5 to 0.6 mg/mL of soluble...
proteins, the major components of which are albumin and transferrin. In diseases such as proliferative vitreoretinopaty or proliferative diabetic retinopathy, the total amount of soluble protein may increase up to 3 times the normal concentration. Elevated intraocular levels of IgG and albumin are observed in rabbits with experimental uveitis induced by intravitreal injection of human serum albumin. Patient 1 may be the first reported human case of autoimmune uveitis with elevated intraocular concentrations of IgG, IgM, and albumin.

Since the serum concentration of the immunoglobulins is within normal range, it is likely that there is a local (intraocular) production of IgG and IgM in response to the uveitis in this patient with JRA. The significant increase in concentration is unlikely to be secondary to diffusion or other modes of transport of the immunoglobulins from the serum into the vitreous cavity. Moreover, molecules of significant size like IgM are not likely to cross the blood-brain barrier to enter the eye.

At the time of surgery, patient 1 only had positive flare but no cells in the anterior chamber. Although patient 1 did not have active inflammation by clinical examination, the vitreous still possessed a large amount of monoclonal IgG antibodies. Such levels may be the residual amount, as the IgG response is usually long lasting, suggesting that there might be even a greater concentration during periods of active inflammation.

Recently, Ronday et al, using immunofluorescence and enzyme-linked immunosorbent assays, have shown that there is elevated intraocular production of IgG and IgA antibody in patients with ocular toxoplasmosis. The authors suggest that the determination of elevated IgA production may be useful as an additional test in the diagnosis of ocular toxoplasmosis. Our results suggest that there was intraocular production of monoclonal antibody in this case of chronic JRA-associated uveitis; they may be produced locally or intraocularly as a nonspecific response to the JRA-associated

**Figure 2.** Immunofixation electrophoresis of the serum of the patient with juvenile rheumatoid arthritis–associated uveitis. It illustrates the normal polyclonal nature of the immunoglobulin (Ig) class of immunoglobulins as revealed by anti-IgG antisera, and the normal polyclonal nature of both kappa (κ) and lambda (λ) light chain containing immunoglobulins as revealed by anti-κ and anti-λ antisera, respectively.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Vitreous, mg/dL</th>
<th>Immunofixation Electrophoresis of Vitreous Fluid</th>
<th>Serum, mg/dL</th>
<th>Immunofixation Electrophoresis of Serum Fluid</th>
</tr>
</thead>
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<tr>
<td></td>
<td>IgG</td>
<td>IgA</td>
<td>IgM</td>
<td>Albumin</td>
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<tr>
<td>1</td>
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<td>28</td>
<td>42</td>
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</tr>
<tr>
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<td>&lt;7</td>
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</tr>
<tr>
<td>5</td>
<td>1.7</td>
<td>&lt;7</td>
<td>&lt;4</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*REM indicates restricted electrophoretic mobility; NT, not tested; and NA, not available.*
ocular inflammation. Alternatively, these monoclonal immunoglobulins may be synthesized in response to specific ocular antigens, which may be present and possibly amplified in patients with JRA. Analyses of vitreal composition of other patients with JRA-associated uveitis, especially those with chronic disease and vitreal schlieren appearance, will be helpful in determining if our findings are an isolated event or if local intraocular production of monoclonal antibody is a characteristic of JRA-associated uveitis.

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