Idiopathic Recurrent Neuroretinitis

Effects of Long-term Immunosuppression

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Objective: To determine the efficacy of long-term immunosuppressive therapy in patients with recurrent idiopathic neuroretinitis.

Methods: A retrospective review of 30 patients with recurrent idiopathic neuroretinitis identified 7 who received ongoing immunosuppression with prednisone and/or azathioprine for whom adequate follow-up information was available. We calculated the number of attacks per unit of time for each patient before and after treatment to derive mean attack rates for the group.

Results: For the entire group, we found a rate of 0.58 attacks per year prior to the initiation of immunosuppressive treatment, which decreased to 0.16 attacks per year following immunosuppression. This represents a reduction in the attack rate of 0.42, or a 72% decrease in attack frequency.

Conclusions: Our study suggests a possible role for long-term immunosuppressive treatment in patients with recurrent idiopathic neuroretinitis. A longer follow-up interval, more standardized treatment regimens, and additional outcome measures might reveal a greater benefit of treatment.


Neuroretinitis (NR) is characterized by acute monocular visual loss with optic disc edema and macular star formation. The most common cause of NR is cat-scratch disease, accounting for two thirds of cases. Additional causes vary and include toxoplasmosis, leptospirosis, mumps, herpes simplex virus, salmonella, tuberculosis, Lyme disease, and syphilis. Despite thorough evaluation, approximately one quarter of cases remain idiopathic.

Although the causes are varied, most patients with NR tend to share a similar clinical profile. The onset is typically acute and painless. In most cases, visual loss is largely due to macular edema rather than optic nerve dysfunction. Thus, relative afferent pupillary dysfunction is either absent or small, and visual field loss takes the form of a central or cecocentral scotoma. Visual recovery parallels the resolution of macular edema and exudates; therefore, the visual prognosis is excellent. Most of these patients experience a single episode of visual loss.

In contrast, a subset of patients with NR have a different clinical profile characterized by disc-related visual field defects, a moderate to large relative afferent pupillary defect, and poor visual outcome. These patients frequently experience recurrent episodes involving the same eye, fellow eye, or both. The cause of this disorder has not been identified and has simply been termed recurrent idiopathic NR. Although laboratory testing has revealed no systemic disease in these patients, some researchers suspect an autoimmune disorder involving the optic disc vasculature.

Treatment of the acute attack (eg, with steroids and/or antibiotics) has been unsuccessful in reversing visual loss. With recurrent attacks, visual loss is cumulative and may result in severe and permanent disability. We therefore sought a form of prophylactic therapy that might prevent additional episodes. To this end, we treated some of these patients with ongoing immunosuppressive therapy. This study represents a retrospective review of this group of patients to assess the efficacy of such treatment.

METHODS

We reviewed the medical records of 85 patients with NR. Within this group, 30 patients with recurrent idiopathic NR were identified.
All patients were examined by 1 of the authors (V.P. or A.K.) between 1983 and 2001. Criteria for the diagnosis were acute unilateral visual loss with ipsilateral optic disc edema and macular star formation that occurred on 2 or more occasions. Ocular or systemic diseases that might cause the neuro-ophthalmic findings were excluded by history, physical examination, and appropriate laboratory testing.

We identified 7 patients with recurrent idiopathic NR who were treated with ongoing immunosuppression for whom adequate follow-up information was available. The other 23 patients with this disorder were excluded for a variety of reasons. In some, long-term treatment was not recommended because there was a long interval between attacks, visual loss was relatively mild, or both. Also, we were less confident about recommending such treatment in the early years of seeing these patients when less was known about the natural history of this disorder. In others, treatment was recommended but declined by the patient because of concern regarding potential adverse effects or the cost of long-term treatment. In some cases, patients were sent to our center for consultation only, and the physician of record elected not to proceed with long-term treatment.

In all 7 patients, a complete medical history was obtained, and a neuro-ophthalmic examination was performed. All patients had to undergo examinations to determine complete blood cell count, erythrocyte sedimentation rate, and levels of fluorescent treponemal antibodies, antineutrophilic antibodies, and angiotensin-converting enzyme. Chest radiography was also performed. In 6 of 7 patients, Bartonella and Treponema antibody titers were obtained. Four of the 7 had anticyc- dilipin antibodies, and 5 underwent a cerebrospinal fluid examination.

Treatment consisted of low-dose, alternate-day administration of prednisone and/or a daily dose of azathioprine. A complete blood cell count and liver function tests were obtained at baseline and at intervals thereafter. We recorded the onset and duration of treatment and the date of each attack both before and after initiating immunosuppressive treatment. For each patient, we calculated the number of attacks per unit of time before and after treatment to derive individual attack rates. We then combined these values to derive mean attack rates for the group.

In addition to long-term immunosuppressive treatment, all patients received intervention for acute attacks consisting of oral prednisone (60-80 mg/d for 1-3 weeks) and/or intravenous methylprednisolone (1 g/d for 3 days). This short-term treatment was given for attacks that occurred both before and after the initiation of long-term immunosuppression.

The numbers of pretherapy and posttherapy attacks were compared using a Poisson regression model within the generalized estimating equation methodological framework. This model included the pretherapy and posttherapy follow-up times as an offset variable to adjust for differences among these times. The generalized estimating equation method was necessary to correlate the pretherapy and posttherapy data for each subject.

The patient group consisted of 3 men and 4 women. Age at onset ranged from 27 to 40 years (mean age, 34.1 years). No patient was found to have any systemic or ocular disease that might cause the neuro-ophthalmic findings. Results of laboratory testing were normal or negative. Demographic data and a record of attacks across time are shown in the Figure.

The follow-up interval from the time of the first attack ranged from 2.2 years to 22.6 years (mean, 12 years). Our patient group experienced 26 episodes of NR during 45.2 patient-years before treatment was initiated. Patients started receiving long-term immunosuppression following 2 or more attacks. In 2 cases, treatment was started after 2 attacks, in 1 case after 3 attacks, in 3 cases after 4 attacks, and in 1 after 7 attacks. Treatment consisted of 50 to 150 mg/d of azathioprine and/or 10 mg of prednisone on alternate days. Four patients were treated with both azathioprine and prednisone, 1 with azathioprine alone, and 2 with just prednisone. Duration of follow-up after the initiation of treatment ranged from 1.4 to 14.5 years (median, 5.8 years; mean, 5.6 years).

Following treatment, the patient group experienced 6 episodes of NR during a period of 39.3 patient-years. For the entire patient group, we found a rate of 0.58 attacks per year prior to immunosuppressive treatment, which decreased to 0.16 attacks per year following the initiation of therapy (Table). This represents a reduction in the attack rate of 0.41 per year with the use of long-term immunosuppression (95% confidence interval, 0.24-0.50), amounting to a 72% decrease in attack frequency. No patient experienced a serious adverse reaction to treatment. Specifically, no patient developed cataracts, a pathologic fracture, an opportunistic infection, bone marrow suppression, or hepatic dysfunction.

Recurrent idiopathic NR is an uncommon condition in which repeated acute episodes lead to progressive and permanent visual loss. This disorder usually affects young adults and has no predilection with regard to sex. The interval between attacks was quite variable in our series, ranging from 1 month to 9.8 years.

Treatment of the acute attack with either oral or intravenous corticosteroids has not appeared to alter the visual prognosis of this condition. Although the cause of recurrent idiopathic NR has not been elucidated, an autoimmune disorder has been proposed that involves occlusive vasculitis affecting the optic disc. For this rea-
son, we undertook long-term immunosuppression in some of these patients.

Our group of 7 patients experienced a total of 26 episodes prior to the initiation of long-term immunosuppressive treatment. Treatment consisted of azathioprine and/or alternate-day administration of corticosteroids. This treatment regimen was selected based on demonstrated efficacy in other autoimmune disorders in which disease activity is more readily monitored (eg, myasthenia gravis). Follow-up immunosuppressive treatment, the patient group experienced 6 episodes. Expressing this information as attacks per unit of time, we found a mean rate of 0.58 attacks per year prior to treatment compared with 0.16 while patients were receiving long-term immunosuppression. This represents a reduction in the attack rate of 72% after the initiation of treatment.

Although these results appear encouraging, our study has several limitations. First, the patient group was small. This is of particular concern in a condition for which the frequency of attacks (both interindividual and intraindividual) is so variable. For example, patient 7 experienced an 11-year attack-free interval. Had treatment been undertaken early in that period, one might have assumed a favorable response to treatment. Also, the length of follow-up after initiating treatment was variable, and in some cases relatively short (patient 1 has been followed for only 1 year since starting treatment).

In addition to the interindividual variability of the disease, treatment regimens were nonuniform. For example, patients who began treatment after only 2 attacks received alternate-day prednisone therapy alone because of concerns regarding the potential long-term toxicity of azathioprine (patients 1 and 4). In other cases, patients were unwilling to undergo long-term treatment with steroids and were therefore treated with just azathioprine (patients 5 and 6).

Despite these limitations, the results of our study suggest a possible role for immunosuppressive treatment in patients with recurrent idiopathic NR. Several factors might lead to an underestimation of the treatment benefit in our patients. First, the follow-up intervals may not have been sufficient to fully demonstrate efficacy. Second, the immunosuppressive regimen may have been suboptimal in terms of dosage or choice of agents. Finally, our study evaluated only attack frequency, not severity of visual loss. The introduction of other outcome measures may reveal a greater benefit of treatment.

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### Statistical Database Summarizing Attack Frequencies for Each Patient Before and After the Initiation of Long-term Immunosuppression

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Total Frequency per Unit of Time, mo</th>
<th>Frequency per Unit of Time (Pretherapy), mo</th>
<th>Frequency per Unit of Time (Posttherapy), mo</th>
<th>No. of Attacks (Pretherapy)</th>
<th>No. of Attacks (Posttherapy)</th>
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<td>271</td>
<td>202</td>
<td>69</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>1015</strong></td>
<td><strong>543</strong></td>
<td><strong>472</strong></td>
<td><strong>26</strong></td>
<td><strong>6</strong></td>
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</tbody>
</table>

Mean Range, mo 26-271 9-202 17-174 2-7 0-2

*For patient 6, frequency per unit of time (posttherapy) is considered uniform even though the therapy was received intermittently.

### References