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The Crisis in Scholarly Publishing: Open Access to the Rescue?

Gale A. Oren, MILS, AHIP

The world of scientific publishing is in crisis. Traditionally, research has been funded by the National Institutes of Health (NIH) and other funding sources. Research is conducted and reported by investigators, who submit their intellectual property to publishers. Publishers produce and disseminate the work. Libraries, institutions, and individuals pay for access to this scientific information.

This cycle was thrown off in the past two decades as journal prices began to increase astronomically. The cost of serial expenditures in research libraries increased 227% from 1986 to 2002, according to the Association of Research Libraries (1). During the same period, the number of purchased serials increased by only 9%, whereas the consumer price index rose 64% (1). These annual price increases continue while library budgets are remaining stable or being cut. As a result, libraries have been forced to cancel journal subscriptions, reducing the variety of content they are able to provide. As the system has spun out of balance, new models of publishing have taken hold. Authors need to be aware of this crisis, understand their options, and learn to better manage their intellectual property.

In this issue of the Journal, Mower and Youngkin (2) point out ways in which authors had better look out for their interests. In defense of publishers, McMullan (3) discusses the potential conflict between open access to the published scientific literature and issues of copyright, peer review, economics, and government intervention. Here is some background on these issues.

THE PLAYERS

The major players in the scholarly publishing marketplace, such as the publishers, libraries, authors, and funding agencies, are motivated by very different factors.

The publishing world has been buffeted by major restructuring. Mergers and acquisitions have resulted in several “mega-publishers,” including Reed Elsevier (ScienceDirect), Springer (SpringerLink), Taylor & Francis (Informa), Blackwell Publishing (Synergy), and Wolters Kluwer (Ovid). It has been shown that as competition decreases, prices increase (4).

Commercial publishers are driven by profit and stockholder interests. The publishers add immense value and expertise as they manage peer review, marketing and distribution, and online access, in addition to the editing and publishing process.

But publishing economics supersede concerns over dissemination and access. Librarians are concerned chiefly with access. They want the greatest amount of relevant content to be available to their users, but rising costs have become a great obstacle. They are also facing the “big deal,” in which electronic content is licensed rather than purchased. Many publishers aggregate or “bundle” electronic content, offering predetermined packages of titles, further reducing the control librarians have over their collections. Bundling squeezes out funding to purchase subscriptions to journals published by smaller or newer publishers. As prices rise, declining subscription rates have resulted in even higher prices. Libraries end up with less content for more money.
Authors have their own motivations. They would like their hard work to be recognized and made easily accessible to their peers. They also need easy access to their peers’ published work. In the traditional publishing model, authors typically sign over rights to their own work in exchange for publication and then depend on publishers to disseminate their work. But the work of researchers builds upon previous research, with the sharing of cumulative knowledge being one of the foundations of the scientific enterprise. Rising subscription costs and reduced access have created barriers to the flow of scientific information.

University administrators are also stakeholders in this crisis. In an open letter to the higher education community, 25 university provosts encouraged support of legislation for “broadening access to publicly funded research in order to accelerate the advancement of knowledge and maximize the related public good” (5).

Consumers, who pay taxes to support government funding of research, want access to the results of that research when medical needs arise. In response to consumer demand, government sees the need for more widespread dissemination of the research it funds, hence its own efforts in that direction.

OPEN ACCESS
This seemingly out-of-control system has laid the groundwork for the “open access” movement, which incorporates a variety of models under one umbrella.

Open access entails a new model of publishing wherein the author, supported by an institution or funding agency, pays the publishing costs and owns the copyright. The publisher manages the peer review process and publishes directly to the Internet, where content is accessible free of charge to the public. Some of the best known open access publishers are Public Library of Science (PloS) and BioMed Central (BMC). Open access publishers take full advantage of available computing technology to streamline the publishing process.

A variant of open access, more accurately known as “public access,” is a National Institutes of Health (NIH)-driven initiative in which articles are submitted to a publicly accessible repository of published articles. The traditional model of publishing is retained in that the publisher still owns the copyright. Published articles are submitted to the repository after a 6- to 12-month embargo. Participants include PubMed Central (PMC), the NIH-sponsored repository, and HighWire Press (developed in 1995 by Stanford University). Still under development, the United Kingdom’s PubMed Central (UKPMC) has recently joined in. In 2004, the NIH stopped short of requiring that NIH-funded articles be submitted to the repository. However, in late 2007, President Bush signed into law the requirement for a mandatory public access policy.

Despite much pressure from researchers, the European Commission still hesitates to mandate that publicly funded research be accessible to all. However, the United Kingdom’s Wellcome Trust, the largest non-governmental research funding entity, requires that articles based on its funding be placed in PMC within 6 months.

Many publishers have developed their own initiatives involving open access, public access, or their hybrids. In July 2006, Elsevier implemented a policy in which all NIH-funded articles are automatically deposited into PMC 12 months after publication unless the author requests otherwise. Springer has introduced an “open choice” program in which authors have the option of paying $3,000 per article for publication costs in return for retaining the copyright. Lippincott Williams & Wilkins has adopted a “delayed” public access policy for the quarterly Journal of Neuro-Ophthalmology, in which all issues are available free online 18 months after publication.

Self-archiving entails having authors submit preprint versions of their work to institutional archives and repositories or posting them on personal homepages. Most publishers allow this, but with distinctive rules and restrictions guiding the process. Institutions are encouraging faculty to self-archive, and it is anticipated that the numbers of authors doing so will increase.

IMPACT FACTOR
It has been claimed that open access articles have a citation advantage: the more accessible the article, the higher its likelihood of being read and cited (6,7). The 2006 impact factors for PLoS Biology and PLoS Medicine were 14.101 and 13.750, respectively, high enough for them to be regarded as top-tier journals. PLoS Biology had by far the highest impact factor among all biology journals ranked for 2006. PLoS Medicine ranked fifth among 103 general and internal medicine journals (8).

On the other hand, a 2004 study done by Thompson ISI, the publisher that calculates and publishes the journal impact factors, showed similar impact factors among open access and traditional journals (9,10). Whether or not opponents approve, it is clear that open access articles are being read and cited and are at least holding their own, if not exceeding citation rates of traditional articles.

ADVANTAGES AND DISADVANTAGES OF OPEN ACCESS AND PUBLIC ACCESS
Apart from free access to readers, other advantages of the open access model are quicker turnover time to publication and higher exposure for authors. But opponents argue that the model is not financially viable in the long term and that it places an unfair financial burden on authors.

The rigor of the peer review process in open access is also questioned. The author-pays model may not only
change the economics, but it also could also influence the traditional peer review process. In addition, in many cases self-archiving is allowed before peer review, which can be confusing. Some open access publishers actually welcome a change in the traditional peer review process. *PLoS ONE* streamlines peer review, leaving part of it up to readers after publication. However, the large majority of open access publishers appear to uphold the usual standards.

Supporters of public access argue that research supported by taxpayers and institutions should be made available to taxpayers and institutions. They also see value in having a centralized place to retrieve articles. Opponents of public access argue that it has a limited effect because it applies only to NIH-funded work. Publishers are concerned that their income will be eroded as libraries cancel subscriptions in the face of more freely available content.

### SCHOLARLY ASSOCIATIONS AND SOCIETIES

Associations and societies have been experimenting with various open access models. For example, the *Proceedings of the National Academy of Sciences of the United States of America* (PNAS) and *The New England Journal of Medicine* now offer free content online 6 months after publication. PNAS also offers an author-pays model for immediate open access. Although scholarly societies certainly benefit from maximizing access to their research, most are dependent on subscription (and membership) income, which is tied to society journals. The Association of Learned and Professional Society Publishers (ALPSP) has cautioned that scholarly societies need to take into account the hidden costs of open access (11).

### CURRENT STATUS

The initial voluntary submission rate of articles to PMC had been disappointing, but this will all change soon because on December 26, 2007, The Consolidated Appropriations Act (HR 2764) was signed into law (12). It includes a provision that directs the NIH to adopt a mandate to provide the public with open access to all NIH-funded research. At the time of the writing of this article, there is still much to be determined as to the timeline and logistics of the mandate, but this act definitely gives the open access movement new momentum.

Publishers continue to fight back. Earlier in 2007, The American Association of Publishers hired a consultant to launch a public relations campaign against open access (13). Because many traditional publishers believe that the open access movement has serious financial implications for the industry, they are compelled to confront it. It remains to be seen what action, if any, will be taken to oppose implementation of the public access new mandate.

### THE FUTURE OF OPEN ACCESS

Librarians believe that open access, in one form or another, is here to stay (14). Peter Suber, the editor of the SPARC Open Access Newsletter, cites as proof the ever-increasing number of open access initiatives, journals, repositories, and policies, as well as publishers’ recognition of this reality and their experimentation with various open access and hybrid models (15). Before passage of the NIH legislation, he had predicted that it would pass and would gradually lead to other funding agency mandates. Suber also predicted that publishers will eventually embrace open access and discover ways to benefit from it (15).

It is clear that authors are the key. They are the creators of the scholarly literature as well as its consumers. They should be the final decision makers as to where and how they will publish. Authors reporting the results of NIH-funded research will need to comply with the forthcoming public access mandate. Regardless of the source of funding, they should look beyond getting their work published and take into consideration how accessible it will be to the scientific community after publication.

I believe that open access is becoming firmly entrenched in the scientific publishing marketplace. The motivating factor—the rising cost of journal subscriptions—continues in full force. Readers of the biomedical literature rightly expect to have extensive access to electronic journals in their areas of interest. Open access, in one form or other, is the best way to meet these expectations.

### REFERENCES


3


Frequency of Anti-Retinal Antibodies in Normal Human Serum

Kaori Shimazaki, BS, Guy V. Jirawuthiworavong, MD, MA, John R. Heckenlively, MD, and Lynn K. Gordon, MD, PhD

Background: Anti-retinal antibodies have been described in the context of autoimmune retinopathies and are often presumed to be pathogenic or disease associated. However, full characterization of patterns of anti-retinal antibody reactivity in normal human serum has been limited. The purpose of this work was to identify the profile of anti-retinal IgG antibodies in serum used as controls in laboratory testing.

Methods: Normal human sera used in commercial diagnostic laboratories were tested for the presence of immunoreactivity against soluble human retinal proteins using Western blot analysis of fractionated soluble human retinal proteins. Reactivity was quantified using computerized densitometry, and the level of reactivity was standardized relative to a control positive serum with known reactivity against recoverin.

Results: Some anti-retinal reactivity was observed in the majority of all tested normal sera. Reactivity against one to two protein bands was observed in 33%. Reactivity against five or more distinct bands was observed in 22%. There was a tendency for serum from women to react with three or more protein bands compared with serum from men.

Conclusions: The presence of anti-retinal antibodies is observed in a majority of normal control human sera, suggesting that identification of new candidate retinal autoantigens should be cautiously interpreted and subject to rigorous testing for disease association.

Molecular Biology Institute (SK) and Jules Stein Eye Institute, Department of Ophthalmology (GVJ), University of California, Los Angeles David Geffen School of Medicine, Los Angeles, California; Kellogg Eye Center (JRH), University of Michigan, 1000 Wall Street, Ann Arbor, Michigan; and Ophthalmology Section, Greater Los Angeles Veterans Affairs Healthcare System, Los Angeles, California.

This work was presented in part at the North American Neuro-ophthalmology Society Annual Meeting.

K.S. and G.V.J. contributed equally to this work.

Address correspondence to Lynn K. Gordon, MD, PhD, 100 Stein Plaza, Los Angeles, CA 90095; E-mail: lgordon@ucla.edu

Additional studies will aid development of a standardized protocol for validation of potential pathogenic seroreactivity.


Autoantibodies against retina are implicated in immune-mediated visual loss (1–4). Anti-retinal reactivity is observed in cancer-associated retinopathy (CAR), melanoma-associated retinopathy, autoimmune optic neuropathy, and a subset of patients with retinitis pigmentosa (5–8). These disorders may be grouped under the heading of autoimmune-related retinopathies (AIRs), a variety of clinical entities classified together according to the presence of immune-associated loss of retinal function.

Although the exact pathophysiological mechanism of this group of disorders is unknown, it has been postulated that the humoral immune response induces AIRs through antibody internalization and interruption of normal cellular physiologic processes resulting in loss of function (1).

The best characterized AIR is CAR (8) in which anti-retinal activity is generated against a retinal protein that is produced by a primary tumor or against a tumor-associated antigen with shared epitopes with a retinal protein (1,9–11). In CAR, antibodies against recoverin, a 23-kDa protein, have been demonstrated to induce retinal cell death through a pro-apoptotic pathway, a likely cause of the eventual retinal dysfunction (11–15). Other antigenic targets have been implicated in the etiology of CAR and other AIR syndromes (3,5,16). Some of the characterized retinal antigenic targets include α-enolase (46 kDa) (12,17), carbonic anhydrase II (30 kDa) (6), recoverin (23 kDa) (18), collapsin response-mediating protein-5 (CRMP-5) (62 kDa) (19), heat-shock protein 70 (65 kDa) (20), tubby-like protein 1 (78 kDa) (21), and lens epithelium-derived growth factor (LEDGF) (22). Other candidate proteins with defined molecular sizes of 22 kDa (23), 40 kDa (24), and 50 kDa (25) have not been formally identified. Despite the interest in this area, anti-retinal reactivity is not universally observed in patients who present with CAR-like signs and
symptoms. On the other hand, anti-retinal antibodies have been demonstrated in some patients with cancer in the absence of any documented visual loss or typical symptoms of an AIR (16,26,27). This observation suggests that the presence of reactivity of one or multiple autoantibodies is either insufficient to induce the disease phenotype or that reactivity may be a preclinical disease marker.

The prevalence of reactivity against these antigens has not been well characterized in a large control population, and the sensitivity and specificity of the anti-retinal antibodies in relation to AIR disease pathogenesis is still uncertain (5,10,16,17,26,28–31). There is also little standardization regarding the methods of detection of anti-retinal immunoreactivity. Prior studies vary in the species origin of the retinal protein extracts (ranging from rodents to primates), the methods of protein extraction, and the definition of positive reactivity. The purpose of this study was to use a standardized protocol with internal positive controls to define the pattern and frequency of IgG reactivity against soluble human retinal proteins in a panel of human control serum.

**METHODS**

**Serum**

Human serum with high 23-kDa anti-retinal reactivity was used as an internal positive control for Western blot studies (gift of C. E. Thirkill, University of California-Davis, Davis, CA). A commercially available set of normal human sera from random blood bank donors, available for use in clinical laboratories as normal controls, was obtained (TheraTest Laboratories, Lombard, IL). Ninety-two samples of normal sera were used in this study and the sex, age, and ethnicity of the subjects are reported in Table 1.

**Western Blot Analysis**

Retinal tissue extracts, 10 μg per lane, were fractionated by SDS-polyacrylamide gel electrophoresis (PAGE) on Novex 4%-20% Tris-glycine gels (Invitrogen, Carlsbad, CA). Proteins were transferred to nitrocellulose membranes (Amersham Life Sciences, Buckinghamshire, UK) overnight in Tris-glycine buffer (National Diagnostics, Atlanta, GA), and adequacy of transfer was verified by ponceau S red staining (Sigma). The membrane was blocked in 5% nonfat milk in PBS-0.1% Tween 20 (PBS-Tween) (Pierce Biotechnology, Rockford, IL) for 2...

**TABLE 1. Characteristics of normal donors**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Age (years)</th>
<th>16–20</th>
<th>21–30</th>
<th>31–40</th>
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<td>4</td>
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</table>

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Anti-Retinal Antibodies

this study (data not shown), and to optimize testing the sera were from individuals of Caucasian ethnicity (American, Asian, Caucasian, and Hispanic), the majority of which were drawn from individuals of various ethnicities (African American, Asian, Caucasian, and Hispanic). Although sera ranged from 16 to 70 years; however, the majority of individuals tested were younger than age 40. Although sera were initially used to reduce background or nonspecific reactivity, and this protocol was optimal (data not shown). Blots were incubated for 1 hour with human sera or with positive control serum (high 23-kDa anti-retinal activity) at a dilution of 1:1000 in 1% nonfat milk in PBS-Tween. In each experiment one lane was used as a secondary antibody control. After multiple washes with PBS-Tween, bound human IgG was identified by horseradish peroxidase (HRP)-conjugated goat anti-human IgG (Pierce) at a dilution of 1:1000 in 1% nonfat milk in PBS-Tween. The secondary antibody was chosen to specifically detect human IgG antibodies. Reactivity was visualized using the sensitive technique of enhanced chemiluminescence (ECL) (Amersham).

Semiquantitation of Immunoblots

Densitometric quantification of anti-retinal reactivity was performed using the Personal Densitometer SI (Amersham) followed by ImageQuant (Molecular Dynamics, Sunnyvale, CA) (Fig. 1). Intensity of the anti-retinal reactivity of the 23-kDa positive control serum was used as an internal control in each Western blot experiment to control for reactivity. Positive reactivity in the tested serum was defined as greater than or equal to 50% intensity of reactivity of the positive control at 23 kDa. Bands identified as human IgG light chain (~25 kDa) or heavy chain (~50 kDa) are often seen in human tissue extracts when probed with a secondary antibody that recognizes human IgG; these specific bands were excluded from additional analysis or comment.

Statistical Analysis

Comparison of the groups of normal sera by gender and number of reactive bands was statistically analyzed by the likelihood ratio \( \chi^2 \) test and Fisher's exact test. A \( P \) value of \( \leq 0.05 \) was considered significant.

RESULTS

Ninety-two human sera samples, commercially used for diagnostic laboratory controls, were screened for anti-retinal antibodies directed against human retinal antigens. Forty-five (49%) samples were from men and 47 (51%) samples were from women. The ages of the individuals ranged from 16 to 70 years; however, the majority of individuals tested were younger than age 40. Although sera were drawn from individuals of various ethnicities (African American, Asian, Caucasian, and Hispanic), the majority of the sera were from individuals of Caucasian ethnicity (Table 1). We initially tested a variety of dilutions of sera for this study (data not shown), and to optimize testing a 1:10000 dilution, which both minimized background and disclosed distinguishable reactive bands, was selected for use in this study.

ImageQuant Western blot analysis detected the presence of anti-retinal IgG immunoreactivity, defined as being equal to or greater than half of the reactivity of the control anti-recoverin serum, in 57 of 92 (62%) normal sera. Thirty (33%) had reactivity against only one or two retinal protein bands, whereas 20 (22%) were reactive against five or more retinal protein bands (Table 2). Although 18 tested women had three or more reactive bands compared with only 9 tested men, this gender difference did not reach the level of statistical significance (\( P = 0.052 \) by likelihood ratio \( \chi^2 \) analysis). There were no significant gender or age differences in sera exhibiting reactivity compared with sera with no anti-retinal reactivity (\( \chi^2 \) or Fisher’s exact test).

The numbers of observed immunoreactive bands varied widely among the different sera tested. Half of the sera with positive anti-retinal reactivity demonstrated only one or two bands of reactivity (Fig. 2). However, five sera exhibited reactivity against at least 10 distinct protein bands, suggesting that a broad range of serum reactivity may be observed in selected control sera. The molecular weights of the observed anti-retinal reactivity also varied widely (Fig. 3). Reactivity is presented in arbitrary units relative to intensity of the anti-recoverin control where equivalent reactivity is 1.00. The observed calculated molecular weight of detected protein bands ranged from 13 to 148 kDa, and reactivity intensity ranged between 0.59- and 1.71-fold of the anti-recoverin control. There were five distinctive clusters of reactivity observed in the tested sera, which may represent common reactivities against the same protein or against multiple proteins with similar size. Notably, reactivity against a 23 kDa retinal protein, presumed to be recoverin, was not detected in any of the 92 sera tested.

DISCUSSION

The present work, using a highly sensitive ECL method for detection and formal densitometric quantification, reveals that the majority of “control normal” sera carry IgG antibodies that are able to react against solubilized human retinal proteins and that Western blots against whole tissue extracts may be of limited utility in determining potential pathogenic auto-reactivity in human subjects.

Although most reports of disease-associated anti-retinal antibodies include a comparison against laboratory normal controls, standardization in these protocols and characterization of normal subjects evaluated in these studies are often unspecified. It has been observed previously that normal individuals may have some antibody reactivity to retinal antigens as detected by Western blot.
**FIG. 1.** Densitometric analysis of Western blots using ImageQuant.  
**A.** For each gel lane a vertical line is placed manually, and the relative density and band position were generated through the ImageQuant program. Lane 1, the secondary antibody only, reveals the IgG heavy and light chain antibodies present in the tissue extract. Lanes 2 and 3 represent IgG reactivity from two different control samples. Lane 4 demonstrates the 23-kDa reactivity in the control positive serum with known reactivity against recoverin.  
**B.** The molecular weight of each measured band is calculated using the position relative to known markers. The bands at 25 and 50 kDa were constantly seen in all lanes and reflect IgG heavy and light chains present in the soluble protein extracts from human tissue. Thus, reactivity at these molecular weights was not used for the determination of the anti-retinal reactivity in the tested sera.
TABLE 2. *Anti-retinal reactivity by sex and age*

<table>
<thead>
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<th>Number of reactive bands</th>
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<th>3-4</th>
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<tr>
<td><strong>Age (years)</strong></td>
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<td>Range</td>
<td>16-60</td>
<td>16-70</td>
<td>20-51</td>
<td>18-52</td>
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Analysis (7–11). Circulating autoantibodies are often observed in human subjects and may result in part from cell degradation and exposure of self-antigens to the immune system (7). One report indicates that a large percentage of patients with visual problems (43%) have circulating anti-retinal antibodies (32). The pathogenetic significance of these antibodies must be questioned in light of our findings of anti-retinal reactivity in the majority of samples in the panel of commercially available normal sera.

Detection and identification of autoimmune retinal antigens using sensitive detection methods often lead to complex patterns of immunoreactivity in both patient and normal control sera. To reveal true potential disease-associated reactivity, one has to develop a system to amplify the signal-to-noise ratio. According to the data presented in this paper, definition of new candidate anti-retinal reactivity against whole retinal extract in a patient population would need to meet specific criteria in comparison with the pattern of reactivity observed in controls. For example, our data show that although the majority of normal sera have some reactivity against human retinal proteins, five clusters of activity against proteins of similar molecular weight are present, and there is large variability in the degree of reactivity against retinal proteins. On the basis of these observations, an unknown serum sample could be identified as having potentially abnormal anti-retinal antibodies if the antigen was of a size not recognized by any of the control panels. Alternatively, preliminary identification of a potentially abnormal anti-retinal reactivity of a specific molecular size such as 23 kDa recognized by both the test and the control serum could be made if the intensity of reactivity in the test serum were much higher than the intensity of reactivity in the control serum. Validation of the reactivity as abnormal would then require other confirmatory methodology. Subsequent validation could be performed by serial dilutions of the test serum to define a titer of reactivity. Other formal characterization of potentially abnormal reactivity should be performed using purified candidate antigens from the retina or by identifying new candidate antigens through Western blots of retinal proteins separated by two-dimensional gel electrophoresis followed by proteomic analysis.

The present study has some limitations. Although it is possible that the high level of anti-retinal reactivity observed in this population is secondary to the sensitivity of the detection method, it is also possible that these samples, drawn from a commercial source, came from individuals with some medical histories that predisposed them to development of autoantibodies. We consider this confounder to be unlikely, as most autoimmune retinopathy occurs later in the life, and the sera used in the present study came from relatively young subjects. Despite this potential limitation, analysis of our data did not reveal prominent changes in antibody patterns with aging although additional studies with a larger control cohort population of older individuals might provide additional information.

**FIG. 2.** Anti-retinal reactivity in normal serum. A distribution of anti-retinal reactivity of normal sera was plotted according to the number of highly reactive bands detected by Western blots. Of 92 human sera tested, 57 showed reactivity against human retina. Although most of the sera tended to have a small number of reactive bands, reactivity against multiple retinal proteins was observed in a small group of sera.
potential limitations suggest that our observations should be validated in a larger control group with detailed medical history and ophthalmic evaluation.

Methods for identifying potential disease-associated anti-retinal reactivity should be carefully defined in prospective studies that include a large, well-defined control population. These methods may include preliminary screening evaluation of reactivity against a whole retinal extract, followed by additional testing and analysis. Validation could be performed against defined candidate antigens; alternatively, an initial screening for specific reactivity could be performed against defined candidate antigens using other techniques, such as proteomic analysis (reviewed in ref. 33), enzyme-linked immunosorbent assay (ELISA) (16,34), defined Western (16,34) or dot blot (34), or antigen arrays (reviewed in ref. 35), for detection of disease-associated antibodies. Our work suggests that, when tested using sensitive methodology, the prevalence of anti-retinal antibodies is high in a test control population and that determination of disease-associated pathogenic autoantibodies requires rigorous standardization through use of an appropriate and large, clinically defined, and validated evaluation.

Acknowledgments

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Histopathologic Features of Multiple Myeloma Involving the Optic Nerves

Sonia N. Yeung, MD, PhD, Katherine E. Paton, MD, Katerina Dorovini-Zis, MD, Jason B. Chew, MB, ChB, and Valerie A. White, MD, MHSc

Abstract: We report a case of optic nerve involvement by multiple myeloma in which progressive visual loss heralded leukemic transformation and intracranial involvement. Imaging showed enhancing nodules in the intracranial segments of both optic nerves posterior to the optic canals and in the anterior optic tract, optic chiasm, and basal leptomeninges. Postmortem histopathologic examination disclosed malignant plasma cells in the subarachnoid spaces around the optic nerves and in the optic nerves. Infarctions were present in both optic nerves near their junction with the globes. Microscopic examination also showed malignant plasma cell infiltration of the leptomeninges of the cerebrum, brain stem, optic chiasm, pituitary gland, cranial bone marrow, and subarachnoid blood vessels. This is the first reported histopathologic examination in conjunction with MRI of multiple myeloma involving the anterior visual pathway. The mechanism of optic neuropathy in this case is probably related to infiltration of the optic nerve meninges by malignant plasma cells and impaired vascular supply caused by aggregated intraluminal plasma cells and monoclonal hypergammaglobulinemia.

CASE REPORT

A 69-year-old man was referred to the Ophthalmology Department at Vancouver General Hospital in April 2004 with a 10-day history of painless progressive blurring and dimming of vision in both eyes. Ten days earlier, visual acuity had been 20/50 in the right eye and 20/40 in the left eye. He also noted that colors appeared washed out to both eyes. He denied double vision and headache. There was no other significant ophthalmologic history.

The patient's medical history included a 1997 diagnosis of multiple myeloma, initially presenting with anemia and plasmacytosis. For the next 6 years, he had undergone treatment with melphalan, prednisone, thalidomide, repeated courses of cyclophosphamide with dexamethasone, and irradiation to his sternum. In 2004, his hemoglobin was falling, and all chemotherapy was withdrawn. Even so, his general medical condition remained stable. He had also been treated for squamous cell carcinoma in situ in the perianal area by irradiation many years earlier. At the time of presentation, the patient was taking no prescribed medications and had no medication allergies.

Our examination showed a best-corrected visual acuity of hand movements in the right eye and 20/200 in the left eye. Confrontation visual fields showed a small preserved superotemporal visual field in the right eye and a preserved peripheral visual field in the left eye. There was a right relative afferent pupil defect. Extraocular movements were full. There was no ptosis, demonstrable orbital masses, or color changes in the surrounding skin. There...
were no bony changes around the orbital margin and no proptosis. Eye movements were full, and the eyes were aligned. The cornea was clear, and the anterior chamber was quiet in both eyes. Intraocular pressures were normal, and fundus examination was completely unremarkable bilaterally. The history and clinical examination suggested an optic nerve or chiasmal process.

MRI of the brain and orbits demonstrated multiple enhancing nodules in the intracranial segments of both optic nerves just posterior to the optic canals (Fig. 1A), in the left optic tract anteriorly, surrounding the left optic nerve immediately posterior to the globe, and around the chiasm. Multiple scattered additional nodular enhancing leptomeningeal deposits were noted (Fig. 1B), including one in the interpeduncular space. Lesions were also seen within the cerebellum and within the left fifth cranial nerve lateral to the pons.

The patient's monoclonal peak was 56 g/L (normal 0 g/L; IgG), hemoglobin was 80 g/L (normal 133–165 g/L), and platelet count was 45 × 10^9/L (normal 150–400 × 10^9/L). A peripheral blood smear showed plasma cells, and the diagnosis of plasma cell leukemia was made. Plasmapheresis was performed. The next day, a lumbar puncture showed malignant plasma cells in the cerebrospinal fluid (CSF). He was subsequently treated for 5 days with whole brain x-irradiation and dexamethasone. Given the known poor prognosis of plasma cell leukemia (3), systemic therapy with chemotherapy was avoided.

Five days after treatment, visual acuity had recovered to 20/25 in the right eye and 20/30 in the left eye. It remained at that level until 1 month after his presentation to the Ophthalmology Department, when his overall condition deteriorated rapidly and he died.

HISTOPATHOLOGIC STUDY

The autopsy was limited to the head. There was infiltration by malignant plasma cells of the subarachnoid spaces around the optic nerves and of the optic nerves themselves (Fig. 2A–B). Tumor cells stained strongly for IgG immunoglobulin (Fig. 2C). Small bilateral wedge-shaped infarctions of the proximal optic nerves were present approximately 2.8 cm posterior to the globe (Fig. 2D). These showed infiltration by macrophages and loss of axons and myelin (Fig. 2E). In no area was the entire cross-section of the nerves infarcted. Both globes were otherwise histologically within normal limits for age.

Two small lytic lesions in the skull and one lesion in the sphenoid bone were identified. Microscopic examination showed focal infiltration by malignant plasma cells of the leptomeninges of the brain, brain stem, optic chiasm, and pituitary gland (Fig. 2F). Some subarachnoid blood vessels contained intraluminal aggregates of neoplastic

FIG. 1. MRI performed 1 month before death. A. Post-contrast T1 coronal study demonstrates bilateral enhancing lesions within the intracranial optic nerves (arrows) bilaterally. B. Postcontrast T1 axial study demonstrates multiple enhancing leptomeningeal nodules (arrows).
plasma cells (Fig. 2G). The bone marrow was hypoplastic and focally infiltrated by neoplastic plasma cells. Some of the intraparenchymal microvessels in the brain were filled with gram-negative bacteria, indicating terminal septicemia. There was no evidence of metastatic squamous cell carcinoma in the optic nerves or brain.

**DISCUSSION**

Representing 80% of plasma cell neoplasms, multiple myeloma is the most common of the plasma cell dyscrasias, accounting for slightly more than 10% of hematologic malignancies (4). It presents at a median age of 72 years with bone pain, anemia, renal insufficiency, infection, and plasmacytomas (5–7). The most common sites of extraskeletal involvement are the spleen, liver, lymph nodes, and kidneys (2).

Ophthalmic manifestations of multiple myeloma are rare but can be the first sign of disease (8,9). Ocular findings include crystal (10) or copper (11) deposition in the cornea, ciliary body cysts (12,13), and retinopathy of hyperviscosity (14–16). The iris (17,18), conjunctiva (1), or choroid (18) may also be involved. Orbital involvement is rare but can be the first manifestation (2,14).

Plasmacytomas may arise in the soft tissues primarily or in the surrounding bones with secondary orbital invasion. Rodman and Font (2) noted proptosis to be the most frequent presentation of orbital infiltration by multiple myeloma. Other rare presentations include periorbital xanthogranuloma, paraproteinemia-induced myositis, and opportunistic ocular infections (2,13,19).

Optic nerve involvement is extremely rare in myeloma. In 1939, Langdon (20) described a patient with multiple myeloma and “retrobulbar neuritis.” There was no pathologic study, and the retrobulbar neuritis was attributed to toxicity rather than to infiltration. Infiltration of the optic nerves by plasma cells was first reported by Gudas (21) in 1971. In 1974, Dahlmann et al (22) reported a patient with infiltration of the optic nerve by disseminated IgA myeloma. Optic nerve compression from an intracranial plasmacytoma has only rarely been described (23–26). Cavernous degeneration of the optic nerve and generalized amyloidosis has been reported (27). Immune-mediated paraneoplastic optic neuropathy has been postulated in association with myeloma (28). Shimada et al (29) recently reported a case of multiple myeloma associated with bilateral optic neuropathy thought to be due to an effect of high immunoglobulin levels on neural conduction.

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**FIG. 2.** Postmortem histopathologic examination. A. Infiltration of the subarachnoid space of the optic nerve by malignant plasma cells (hematoxylin and eosin; original magnification: ×200). B. Infiltration of the optic nerve by malignant plasma cells (hematoxylin and eosin; original magnification: ×100). C. Plasma cells in the subarachnoid space (anti-light chain, hematoxylin counterstain; original magnification: ×100). D. Small wedge-shaped infarctions of the optic nerve (hematoxylin and eosin; original magnification: ×12.5). E. Loss of axons and myelin in the area of optic nerve infarction (Luxol fast blue/Bielschowsky stain; original magnification: ×100). F. Focal infiltration of the leptomeninges of the brain by malignant plasma cells (hematoxylin and eosin; original magnification: ×400). G. Intraluminal aggregates of neoplastic plasma cells in a subarachnoid blood vessel (hematoxylin and eosin; original magnification: ×100).
Intracranial involvement by multiple myeloma is rare, with an estimated overall frequency of 1% (30). It can present as either an intraparenchymal or leptomeningeal lesion, often with multiple neurologic symptoms and signs. These include altered mental status, cranial nerve palsies, limb weakness, and occasionally the effects of a space-occupying lesion and raised intracranial pressure (31–33). Leptomeningeal spread can occur either by local invasion from the bone or by hematogenous dissemination (34). Obstructive hydrocephalus resulting from leptomeningeal infiltration has also been reported (35). The diagnosis is made by imaging studies and examination of plasma cells within the CSF. The prognosis of myelomatous involvement of the meninges is poor despite the use of aggressive local and systemic treatment (3). This poor prognosis is attributed to the fact that meningeal involvement generally occurs in patients with advanced disease. The average time from onset of neurologic symptoms to death has been reported to be 8 weeks (33).

The pathophysiologic processes that give rise to a majority of the ophthalmic signs are direct infiltration by plasma cells, compression by tumor mass, meningeal metastases, and hematologic abnormalities (12,14,21,36). Hyperviscosity syndrome occurs in multiple myeloma owing to an overproduction of monoclonal immunoglobulin in the bone marrow. As a result, the microcirculation is impaired owing to increases in plasma viscosity.

The mechanism of optic neuropathy in this case is probably related to infiltration of the optic nerve meninges by malignant plasma cells and impaired vascular supply caused by aggregated intraluminal plasma cells and monoclonal hypergammaglobulinemia. Neural conduction in the optic nerves may have also been compromised by excessive IgG, perhaps owing to a humoral mechanism (28,29,37). To what extent the infarctions evident on histopathologic examination accounted for the patient's loss of vision is uncertain, given that plasmapheresis and whole body irradiation in our histopathologic examination accounted for the patient's loss of vision. Focus on the impact of the disease on the optic nerve and the potential for recovery due to treatment.

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High-Titer Collapsin Response-Mediating Protein-Associated (CRMP-5) Paraneoplastic Optic Neuropathy and Vitritis as the Only Clinical Manifestations in a Patient With Small Cell Lung Carcinoma

Edward Margolin, MD, Andrew Flint, MD, and Jonathan D. Trobe, MD

Abstract: Paraneoplastic optic neuropathy (PON) is a rare syndrome usually associated with small cell lung carcinoma. In the 27 rigorously reported cases, neurologic manifestations other than visual loss have been present in all but 2. In the single case in which vision improved in response to treatment of the cancer, the collapsin response-mediating protein (CRMP)-5 titer did not change, and the ophthalmic examination was not detailed. We describe a patient with optic neuropathy and vitritis as the only clinical manifestations of PON marked by an extremely high titer of CRMP-5 antibody. Treatment of the underlying small cell lung cancer coincided with resolution of the visual abnormalities and a dramatic decrease in the CRMP-5 titer.

CASE REPORT

A 67-year-old woman had a 6-month history of slowly progressive visual loss in both eyes. She reported fatigue during the same period but no other symptoms. She had smoked a pack of cigarettes daily for the past 30 years. Best-corrected visual acuity was 20/70 in the right eye and finger counting in the left eye. There was no relative afferent pupillary defect. Ophthalmoscopy revealed moderate vitreous cells and optic disc swelling bilaterally (Fig. 1). Humphrey visual fields revealed a mean deviation of 15 dB in the right eye and 15.8 dB in the left eye without localizable features (Fig. 2). Results of the neurologic examination were otherwise normal.

Results of MRI of the brain and orbits were normal. Lumbar puncture revealed a normal opening pressure and a normal cerebrospinal fluid (CSF) formula except for a mildly elevated protein level of 56 mg/dL. Serum and CSF angiotensin-converting enzyme (ACE), Bartonella henselae, Toxoplasma gondii, Borrelia burgdorferi, herpes simplex virus (HSV), herpes zoster virus (HZV), syphilis, HLA-B27, HLA-A29, purified protein derivative (PPD), Bartonella titers, and lysozyme levels were normal.

Retinal fluorescein angiography revealed mild late optic disc leakage in both eyes (Fig. 3). CT of the chest, abdomen, and pelvis disclosed lymph node enlargement involving the right hilum and subcarinal regions but no other abnormalities (Fig. 4). Bronchoscopy with needle aspiration was nondiagnostic. A 3-day course of 1 g/day intravenous methylprednisolone provided no improvement in vision, vitritis, or optic disc edema.
FIG. 1. Fundus photography performed at presentation shows bilateral optic disc swelling and vitreous haze.

A paraneoplastic antibody panel disclosed a CRMP-5 IgG titer of 1:245,760, one of the highest ever reported by the Mayo Clinic Neuroimmunology Laboratory. Based on this finding, the patient underwent mediastinoscopy, which produced frozen sections negative for neoplasm. On permanent section, one of eight lymph nodes demonstrated small cells with fine chromatin and scant cytoplasm. On immunohistochemical analysis, these cells stained strongly and uniformly for CD56 (Fig. 5). The diagnosis of small cell lung carcinoma was finally made.

Staging with positron emission tomography revealed increased uptake limited to the right hilar and subcarinal lymph nodes. Neurologic examination continued to reveal no abnormalities.

Treatment with carboplatin and etoposide and concurrent radiotherapy was started. Five months after the initiation of treatment, a repeat CT of the chest demonstrated a decrease in the size of the hilar lymphadenopathy and complete resolution of subcarinal lymphadenopathy (Fig. 6).

At a follow-up neuro-ophtalmologic visit 6 months after the initial presentation, visual acuity was 20/20 in each eye. Ophthalmoscopy disclosed very mild optic disc pallor in both eyes but no vitreous cells and complete resolution of optic disc edema (Fig. 7). Humphrey visual fields revealed a mean deviation of 4.4 dB in the right eye and 6.4 dB in the left eye (Fig. 8). The CRMP-5 IgG titer had fallen to 1:30,720.

DISCUSSION

We have described a patient with PON and vitritis in small cell carcinoma of the lung, a diagnosis not suspected until CRMP-5, a paraneoplastic antibody associated with this cancer, was discovered.

Among the previously reported cases of CRMP-5-positive PON and vitritis, our case is exceptional in that the CRMP titer was extremely high, yet the patient had no other neurologic abnormalities. Only two cases of CRMP-5-positive PON have been previously described in which patients lacked other neurologic deficits: in one case, the CRMP-5 titer was not reported (3); in the other, the titer did not change in response to treatment (6).

Our case is unique in that the patient's CRMP-5 titer decreased significantly in response to chemotherapy and radiotherapy, a phenomenon not previously described. It is also the only rigorously reported case of resolution of optic nerve swelling and vitritis with normalization of visual acuity after the initiation of chemotherapy and radiotherapy for the underlying cancer.

CRMP-associated PON typically presents as subacute visual loss in both eyes with optic disc swelling.

FIG. 2. Humphrey visual fields performed at presentation show multiple high thresholds without a localizable configuration to the defect. Mean deviations are -15 dB in the right eye and -15.8 dB in the left eye.
FIG. 3. Late-phase retinal fluorescein angiography performed at presentation shows bilateral mild optic disc leakage.

FIG. 4. Chest CT performed at presentation shows right hilar lymphadenopathy (A, arrow) and subcarinal lymphadenopathy (B, arrow).

FIG. 5. Histopathology of the mediastinal lymph node biopsy. A. High magnification (×125) hematoxylin and eosin stain shows malignant cells with hyperchromatic irregular nuclei, scant cytoplasm, and nuclear molding. B. CD56 antibody stain for neural cell adhesion molecule has produced diffuse positive brown staining of the cytoplasm of neoplastic cells.
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FIG. 6. Chest CT performed 5 months after presentation shows a decrease in the size of the hilar lymphadenopathy (arrow).

Vitreous cells are frequently present, as in our patient (2,3,7). Most of the previously reported patients, however, differ from ours in having had neurologic accompaniments to their visual loss (2,4,8). These abnormalities have been divided into two groups (2): 1) multifocal encephalomyeloneuropathy (a cerebellar syndrome being a common finding in this group) and 2) myelitis resembling Devic disease (3). As in our patient, the underlying cancer in the vast majority of patients with PON described previously is small cell lung carcinoma (2-5,9,10). However, there are individual case reports of patients with CRMP-5 PON and bronchial carcinoma, thymoma, thyroid papillary carcinoma, renal cell carcinoma, Hodgkin and non-Hodgkin lymphoma, neuroblastoma, pancreatic glucagonoma, and nasopharyngeal carcinoma (4,5,8,9). Interestingly, the patients with a Devic-like presentation have tended to have some of these non-lung cancers (2,8,9,11).

CRMP-5 is an IgG antibody first described in 2001 by Yu et al (5). Malik et al (2) in 1992 had described an antibody in patients with PON that bound only to oligodendrocytes in adult brain. It was later thought to be the same antibody as CRMP-5. CRMP-5 is directed against a 62-kDa neuronal cytoplasmic protein of the collapsin response mediator family. It is expressed in adult central and peripheral neurons, in small-cell lung carcinoma, and rarely in thymoma (5). The CRMP-5 family of proteins is believed to mediate growth guidance cues during embryogenesis (5).

CRMP-5 IgG is not specific for PON. In a recent paper by Cross et al (2), only 16 (9%) of 172 patients with positive CRMP-5 titers had PON; the rest had other neurologic impairments. Up to 35% of patients with positive CRMP-5 titers and small cell lung carcinomas, however, have some neurologic manifestations such as optic neuropathy/retinitis with vitreous cells, other cranial neuropathies, and subacute chorea or other basal ganglia disorders (2,5,10,13). Other previously described neuroophthalmic manifestations have included impaired upgaze, nystagmus, multiple cranial neuropathies, and opsoclonus (3,5). The wide variety of other neurologic abnormalities seen in these patients probably results from the effect of the antibodies on many sites in the nervous system (2,14).

The detection of autoimmune antibodies does not predict a specific neurologic syndrome but rather directs the search toward an underlying cancer, which is present in up to 90% of patients (1,2,14). The cancer is often at an early stage and, in some patients, is hard to find. In our patient, multiple frozen sections of the lymph nodes obtained by mediastinoscopy were read as a “reactive process” and the diagnosis of sarcoidosis was therefore suggested. Only the knowledge of the very high CRMP-5 antibody titer persuaded the pathologist to perform additional sectioning and staining that led to the discovery of the underlying cancer.

FIG. 7. Fundus photography performed 6 months after presentation shows resolution of optic disc edema and vitritis and mild optic disc pallor bilaterally.

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cancer. Diagnosis and treatment of cancer at this early stage can potentially be curative.

It has been hypothesized that the reason for a low tumor burden in these patients is an effective anti-cancer immune host response (1). If true, the use of immunosuppressive medication for the treatment of paraneoplastic disorders might be contraindicated. There is, however, no clinical support for this hypothesis. On the contrary, some patients seem to benefit from immunosuppression with improvement of the paraneoplastic manifestations (1,15). Management of a suspected paraneoplastic syndrome should consist of diagnosis and treatment of the underlying cancer together with the use of immunomodulatory therapy (corticosteroids, intravenous immunoglobulins, and plasmapheresis) in patients who are impaired from the paraneoplastic effects (1,15).

Immunomodulatory treatment of visual loss in PON has, however, been unrewarding (1,18,19). On the basis of very limited success in the treatment of cancer-associated retinopathy (16,17), systemic corticosteroids and intravenous immunoglobulins have been tried in PON (18,19). Even with simultaneous initiation of chemotherapy and radiotherapy, vision has generally not improved and has often deteriorated (2–4). Our case joins two previously reported cases as exceptions to this experience (6,20). One report (6) described limited improvement of visual acuity in a patient who was treated with cisplatin and etoposide for underlying small cell lung carcinoma, but the details of the ophthalmic examination were not presented. Another report (20) highlighted a substantial improvement in visual function after treatment with intravenous methylprednisolone, cisplatin, and VP-16, but baseline visual acuities (20/30 and 20/40) were much better than those in our patient and the exact nature of the paraneoplastic antibodies was not determined.

PON should be included in the differential diagnosis of any patient presenting with optic nerve swelling and vitritis. Discovery of the CRMP-5 antibodies can initiate a search for the underlying malignancy while it is at an early stage and lead to the rapid initiation of treatment, which can be potentially curative. Treating the paraneoplastic manifestations with immunomodulatory agents but without anticancer agents may not necessarily be prejudicial toward cancer survival but is unlikely to benefit the paraneoplastic manifestations.

REFERENCES


Melanoma-associated retinopathy (MAR) is a rare paraneoplastic syndrome occurring in the presence of cutaneous malignant melanoma (1). Patients with MAR commonly develop subacute visual loss within months to years after diagnosis of malignant melanoma of the skin. Symptoms usually include positive visual phenomena, peripheral visual field loss, and night blindness. Electroretinography (ERG) reveals significant scotopic abnormalities with a severely decreased rod-specific response and a negative maximal response. The photopic responses, although much less affected, have a characteristic broadened a-wave trough and sharply rising b-wave peak, suggesting an impairment of the rod ON bipolar cell pathway (2). MAR presumably results from antibodies produced against unknown melanoma-associated antigens that cross-react with retinal bipolar cells leading to defective signal transduction and visual loss (1,3).

Treatment of the visual loss associated with MAR has been disappointing. Use of corticosteroids and chemotherapy has been ineffective (4) with the exception of one patient who had MAR associated with uveitis (5). In a review of 62 patients with MAR, only 7 patients experienced visual improvement after receiving various treatment regimens (2). Four of the 7 patients were treated with metastasectomy and 2 of them with intravenous immunoglobulin (IVIg) therapy. Vision in 1 patient improved with IVIg treatment alone, vision in 1 improved with plasmapheresis and methylprednisolone treatment, vision in 1 improved with radiation treatment to sites of melanoma recurrence (2). We provide the second report of a patient with MAR whose visual function appeared to improve after treatment with IVIg.

CASE REPORT

A 56-year-old man with malignant melanoma of the right temporal forehead area underwent wide excision and lymph node dissection in 2001. The Breslow thickness of the tumor was 0.8 mm, and the Clark level of invasion was 4. Lymph nodes were negative for tumor metastases.

Four years later, in September 2005, the patient complained of blurred vision and flickering lights in the left eye only. The patient reported no night blindness. There were no other medical problems or family history of retinal disorders.

Best-corrected visual acuities were 20/25 in both eyes. Visual field testing revealed constriction in the left eye...
only. Pupillary examination showed a left relative afferent pupillary defect. Dilated fundus examination showed no evidence of vitreous cells, vessel attenuation, pigmentary changes, or optic disc pallor. Results of ERG in the left eye were consistent with MAR, in that ERG showed an abolished rod-specific response, a negative maximal response, and a photopic response with a broadened a-wave trough and a sharply rising b-wave peak. There was complete loss of the ON bipolar activity in the left eye. ERG findings for the right eye were essentially normal, although there was a slight decrease in the b-wave/a-wave ratio of the maximal response and a slight decrease in the ON bipolar ERG findings compared with normal values (Fig. 1). Dark adaptation studies were not performed.

An enlarged right preauricular lymph node (1.3 cm) was then found on physical examination. An excisional biopsy sample indicated recurrent melanoma. CT of the chest, abdomen, and pelvis performed in September 2005 did not show other metastatic disease. In October 2005, to complete optimal treatment for local recurrence, the patient underwent superficial parotidectomy, right modified radical neck dissection, and regional flap reconstruction. Whole body positron emission tomography and CT in December 2005 showed no suggestion of other sites of melanoma. The patient then received 6,000 cGy of external beam irradiation to the right neck including a 1,000-cGy boost to the preauricular region.

Results of a paraneoplastic antibody profile were negative, including the following antibodies: anti-neuronal nuclear type 1, 2, and 3, Purkinje cell cytoplasmic type 1, 2, and Tr, amphiphysin, collapsin response-mediating protein-5 (CRMP-5), striational, calcium channel binding P/Q, acetylcholine receptor, and potassium channel.

Three months after reporting blurred vision and flickering lights in his left eye, the patient reported the same symptoms in his right eye. Best-corrected visual acuities were 20/25 in the right eye and 20/40 in the left eye. ERG demonstrated nearly absent scotopic amplitudes, negative maximal responses, and a broadened photopic a-wave trough with a sharply rising b-wave peak in both eyes, consistent with a diagnosis of MAR. Visual field analysis demonstrated significant defects in both eyes (Fig. 2). Dilated fundus examination remained unchanged with no evidence of vitreous cells, vessel attenuation, pigmentary changes, or optic disc pallor.

The patient received 100 g IVIg for 2 consecutive days and then monthly thereafter. Four weeks after the initiation of IVIg therapy, best-corrected visual acuities had improved to 20/20 in the right eye and 20/30 in the left eye. The visual field improved significantly in the right eye but...
FIG. 2. Humphrey visual fields before intravenous immunoglobulin treatment demonstrate severe bilateral visual field loss (A) and gradual improvement 1 month (B), 2 months (C), and 8 months (D) after treatment was started. Four months after treatment was stopped, visual fields had not worsened (E).

remained poor in the left eye. Over the next 4 months, the patient's visual acuities remained stable, ranging from 20/20 to 20/40 in the right eye and from 20/25 to 20/40 in the left eye. Visual fields continued to improve steadily (Fig. 2). There was no improvement in the ERG (Fig. 3). The IVlg dosing schedule was changed to once every 6 weeks in May 2006. This schedule was again extended to once every 8 weeks in August 2006 because of continued stability of visual acuities and visual fields. The patient received the last dose of IVlg in December 2006. At the last follow-up visit in April 2007, best-corrected visual acuities were 20/20 in the right eye and 20/25 in the left eye. Visual fields continued to show improvement. (Fig. 2) Over the course of treatment, the patient noted progressive improvement in night vision, peripheral vision, and photopsias. He described his visual function as nearly normal with the exception of mild intermittent peripheral vision. During the last 18 months of postoperative follow-up, no evidence of melanoma recurrence or metastatic disease has been found.

DISCUSSION

Our patient is noteworthy because his visual fields improved after IVlg treatment, and although metastasectomy in our patient also could have played a role in this improvement, the recovery in visual fields occurred only after IVlg was started. In previously described patients (2), only one patient showed improved visual function after IVlg treatment alone.

MAR can be caused by antibody production against melanoma-associated antigens that cross-react with analogous epitopes on retinal rod bipolar cells. Neuronal retinal antigen (2), transducin (6), and photoreceptor cell-specific nuclear receptor (7) are documented examples of epitopes recognized by these antibodies. Gold et al (8) have proposed several mechanisms of IVlg action, including an anti-idiotype reaction against membrane-bound B-cell receptor, neutralization of autoantibodies by anti-idiotypes, binding of complement components C1, inhibition of maturation of dendritic cells with consecutive inhibition of T-cell activation, and modulation of the expression of intercellular adhesion molecules. We hypothesize that once IVlg-mediated modulation of the immune system occurs, a permanent cessation of the production of autoantibodies may occur.

Because of the rarity of MAR, it is difficult to evaluate treatments by using prospective, randomized studies. Still, it is widely agreed that decreasing the melanoma tumor burden in MAR with metastasectomy or radiation is an important first-line treatment. In our patient, however, visual function continued to decline for 2 months after surgical removal of the metastatic tumor mass and subsequent radiation therapy. Only after the initiation of IVlg therapy were improvements in visual fields observed in our patient, suggesting that the production of autoantibodies
may continue even after a reduction or elimination of tumor burden.

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Long-Term Survival in Paraneoplastic Opsoclonus-Myoclonus Syndrome Associated With Small Cell Lung Cancer

Khaled A. Hassan, MD, Gregory P. Kalemkerian, MD, and Jonathan D. Trobe, MD

Abstract: Paraneoplastic opsoclonus-myoclonus syndrome (OMS) is associated with small cell lung cancer (SCLC) in adults. Without appropriate treatment for SCLC, all reported patients with SCLC and OMS have died of complications of OMS within 3 months of diagnosis. With appropriate treatment, about half of reported patients have had improvement in neurologic function, and several have become long-term survivors (6–84 months). We report a patient with SCLC who presented with OMS and was refractory to immunosuppressive therapy but responded rapidly to antineoplastic therapy and remains alive with no sign of SCLC recurrence and minimal residual neurologic deficits 30 months after diagnosis. In patients presenting with OMS, early recognition and treatment of the underlying malignancy probably improve the chances for recovery from the OMS with minimal deficit and ultimate survival.

Small cell lung cancer (SCLC) is a poorly differentiated neuroendocrine malignancy characterized by aggressive growth and early metastases. It accounts for 15%–20% of all cases of lung cancer (1). Most patients with SCLC present with extensive-stage disease for which chemotherapy is associated with prolongation of survival, but rarely beyond 2 years. One third of patients with SCLC present with limited-stage disease, defined as disease confined to the ipsilateral hemithorax and mediastinum that can be safely encompassed within one radiation field. In limited-stage SCLC, the goal of treatment is cure. Concurrent administration of platinum-based chemotherapy and radiotherapy results in a 5-year survival rate of 20%–25% (2,3).

The neuroendocrine nature of SCLC accounts for its association with a variety of endocrine and neurologic paraneoplastic syndromes (PNSs). Endocrine PNSs such as syndrome of inappropriate antidiuretic hormone (SIADH) and Cushing syndrome are caused by ectopic secretion of peptide hormones by SCLC cells and are reversible with appropriate anti-cancer therapy. In contrast, neurologic PNSs are caused by an autoimmune response to specific antigens expressed on cancer cells, leading to the production of autoantibodies that cross-react with specific components of the nervous system (4,5). Frequently, these autoantibodies induce neuronal cell death, resulting in progressive and irreversible neurologic dysfunction such as that seen in limbic encephalopathy and subacute cerebellar degeneration. Some autoantibodies merely interfere with neurologic signaling, a derangement that can be successfully reversed with immunosuppression or antineoplastic therapy, as is the case in Lambert-Eaton myasthenic syndrome.

Opsoclonus-myoclonus syndrome (OMS), a rare disorder that is frequently associated with malignancy, is characterized by opsoclonus (spontaneous, arrhythmic, large-amplitude, conjugate saccades occurring in all directions of gaze) and myoclonus (irregular muscular spasms of the head, trunk, or extremities) and sometimes encephalopathy (6). The pathophysiologic basis of OMS is unknown. Neuronal cell loss has not been identified and, in some patients, the clinical manifestations appear to be reversible. It has been suggested that OMS may be due to a disturbance in the inhibitory neurotransmitter system caused by anti-glycine receptor autoantibodies. Sera from patients with paraneoplastic OMS can disrupt the binding of Nova-1/Nova-2 proteins to glycine receptor mRNA, causing deregulation of its expression that may explain the underlying motor dysfunction of OMS (7,8).

Long-term survival of patients with SCLC and paraneoplastic OMS ranges from 6 to 84 months (9,10). We describe a patient with SCLC and OMS who was treated...
with appropriate anti-cancer therapy and remains cancer-free 30 months after diagnosis without significant neurologic sequelae, joining a small number of reported OMS/SCLC patients with neurologic recovery and long-term survival.

**CASE REPORT**

A 57-year-old woman developed diplopia, dysarthria, and involuntary motor activity involving her eyes, head, trunk, and extremities. She was a long-time smoker. Results of brain MRI and electroencephalography were normal. Results of standard blood and serum evaluation and lumbar puncture were unrevealing. CT of the chest, abdomen, and pelvis revealed a 1.5-cm left hilar mass. After 5 weeks of progressive symptoms, she developed respiratory failure requiring mechanical ventilation.

Upon arrival at our institution, she did not respond to verbal stimuli but did withdraw to pain. She had spontaneous random jerking movements of the face, head, and all four extremities. Rapid, random, conjugate eye movements in all directions were noted under closed lids and were present when her eyelids were lifted (see Video, available online-only through ArticlePlus). The right eye was consistently higher than the left eye (attributed to skew deviation). Results of pupil and optic fundus examinations were normal. Deep tendon reflexes were intact, and plantar reflexes were flexor.

We made a clinical diagnosis of paraneoplastic OMS, but results of a comprehensive paraneoplastic antibody panel (Mayo Clinic) were negative. She was treated with intravenous immunoglobulin (IVIg) (1 g/kg initial dose followed by 0.5 g/kg) for 10 days and 1 g methylprednisolone intravenously daily for 5 days followed by 60 mg prednisone daily for 8 days without clinical improvement.

A chest CT repeated 13 days after the initial study showed enlargement of the left hilar mass to 2.5 cm (Fig. 1). Bronchoscopic aspiration biopsy of this mass revealed SCLC (Fig. 2). Results of immunohistochemical analysis were positive for pancytokeratin and CD56 (neural cell adhesion molecule), and negative for leukocyte common antigen. Positron emission tomography with fluorodeoxyglucose showed uptake only in the biopsied left hilar mass.

She was treated with carboplatin and etoposide. Two days later, myoclonus was markedly improved and she was extubated. After a second cycle of chemotherapy, she was discharged from the hospital with normal mental status, no myoclonus, and minimal opsoclonus.

She completed four cycles of chemotherapy followed by thoracic radiotherapy for limited-stage SCLC with complete tumor response and resolution of neurologic signs and symptoms by the end of treatment. Thirty months after her initial diagnosis, she remains cancer-free, and her only residual neurologic symptom is mild tandem gait instability accentuated by fatigue.

**DISCUSSION**

Paraneoplastic OMS is most commonly associated with neuroblastoma in children and with SCLC in adults (11,12). However, it has been reported in association with cancers of the ovary, breast, thyroid gland, and kidney and with Hodgkin and non-Hodgkin lymphoma and melanoma (6,13–17). Paraneoplastic OMS is thought to be antibody mediated. In a study of children with neuroblastoma, those with OMS had significantly higher serum titers of anti-neuronal antibodies (18). The presence of numerous...
anti-neural antibodies, including anti-Hu, anti-Ri, anti-neurofilament, and anti-Purkinje cell antibodies, has been described in patients with paraneoplastic OMS, but none of these has been consistently associated with the clinical syndrome (19–22). Patients with neuroblastoma-associated OMS also exhibit elevated numbers of B lymphocytes in the CSF as well as interstitial or perivascular lymphoid infiltrates containing follicular dendritic cells and B lymphocytes, suggesting a localized immune reaction that can result in antibody production (23,24).

Despite evidence of an autoimmune etiology for OMS and the lack of evidence of neuronal cell death on autopsy studies, immunosuppressive therapy with adrenocorticotropic hormone (ACTH), corticosteroids, IVlg, cyclophosphamide, azathioprine, and plasmapheresis has produced inconsistent clinical improvement (25,26). Clinical improvement has, however, been reported with rituximab, a monoclonal antibody targeting CD20-expressing B lymphocytes (27).

It appears that tumor control is essential for successful long-term management of paraneoplastic OMS. In a series of 14 patients with OMS associated with a variety of tumor types, 6 were treated with IVlg and/or corticosteroids without antineoplastic therapy, whereas the remaining 8 received appropriate treatment for their primary malignancies (9). Five of the 6 patients treated with immunosuppression alone died of progressive OMS within 6 months, whereas the 8 patients who received appropriate anti-cancer therapy all had complete or partial neurologic improvement and only 2 died of progressive malignancy at 11 and 18 months after diagnosis. The remaining 6 patients are alive with follow-up ranging from 6 months to 14 years.

Survival of patients with paraneoplastic OMS varies considerably, depending on the underlying malignancy, but appears to be longer in patients with potentially curable cancers. A relatively long survival rate has been reported in children with neuroblastoma and paraneoplastic OMS compared with children with neuroblastoma unassociated with OMS (28). Korfei et al (29) reported that serum from patients with OMS can inhibit cellular proliferation and induce apoptosis in neuroblastoma cell lines, suggesting that OMS-associated autoantibodies may confer an antineoplastic benefit in patients with neuroblastoma. However, there are no clinical or laboratory data to support such an effect in adult patients with paraneoplastic OMS associated with other tumors.

There have been 18 cases of OMS associated with SCLC reported in the English literature since 1990 (9,10,30–33). Treatment and survival data are available for 15 of these patients (Table 1). Of the 4 patients who did not receive anti-cancer therapy, 3 died of progression of neurologic symptoms within 3 months of diagnosis and 1 died within 5 months with no available cause of death. Of the 11 patients who received anti-cancer therapy, all had substantial improvement of neurologic symptoms. One patient had

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SCLC, small cell lung cancer.
complete resolution of neurologic symptoms and remains alive and asymptomatic 17 months after appropriate anti-cancer therapy (9). Among the remaining 10 patients, 4 remain alive with residual mild neurologic deficits at follow-up ranging from 6 to 84 months, whereas 6 have died, 4 from progressive SCLC (4, 11,18, and 22 months), 1 from sepsis (35 months), and 1 of an unknown cause (3 months).

Thus, before the report of our patient, there had been 5 instances of long-term survival in patients with OMS associated with SCLC reported since 1990. The longest survivor was cancer-free with residual truncal ataxia and mild opsoclonus 84 months after diagnosis (10). The other four patients were alive for 6, 17, 24, and 39 months after diagnosis (9,32). Another patient died 35 months after diagnosis of complications of persistent neurologic debility (33). Overall, only 3 patients with OMS associated with SCLC have been reported to have a survival time longer than that of our patient, who is alive with a mild tandem gait disorder 30 months after diagnosis. IVIg and corticosteroids appeared to have minimal effects on our patient’s neurologic condition. We attribute the nearly complete neurologic recovery and relatively long-term survival to the recognition of OMS as a paraneoplastic phenomenon and the timely diagnosis of the underlying malignancy, which allowed prompt initiation of anti-cancer chemotherapy.

Acknowledgment

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REFERENCES

Third Cranial Nerve Palsy Caused by Intracranial Extension of a Sino-Orbital Natural Killer T-Cell Lymphoma

Celia S. Chen, MBBS, MPH, FRANZCO, Neil R. Miller, MD, FACS, Andrew Lane, MD, and Charles Eberhart, MD, PhD

Abstract: Natural killer/T-cell lymphomas (NKTLs) are rare destructive lesions that usually involve the nasal cavity or paranasal sinuses. Orbital and intracranial involvement is rare. A 53-year-old man with systemic lupus erythematosus who was receiving chronic low-dose prednisone treatment developed proptosis of the right eye. Biopsy of a sino-orbital lesion suggested nonspecific inflammation. Clinical and imaging manifestations resolved with a higher dose of prednisone, but when the prednisone dose was tapered, the patient developed a complete right third cranial nerve palsy. Imaging showed return of the original lesion, now with intracranial extension and enhancement of the right third cranial nerve. Repeat biopsy showed features consistent with NKTL. Biopsy of this lesion in its early stage may misleadingly suggest a primary inflammatory disorder because of a paucity of neoplastic cells, a large number of inflammatory cells recruited by the innate natural killer (NK) cell immune response, and extensive necrosis caused by angiodestructive tumor cells.

The sinuses and nasal cavity are the most common sites of involvement of NKTL. Orbital involvement is infrequent and intracranial spread is rare (3). We describe a case of NKTL that presented as a mass involving the paranasal sinuses and orbit. Initial biopsy of the lesion showed mixed inflammatory cells. The lesion regressed during treatment with systemic corticosteroids but recurred upon tapering of the prednisone dose and subsequently extended intracranially and produced a complete third cranial nerve palsy, at which time repeat biopsy with specialized immunostaining led to a diagnosis of NKTL.

CASE REPORT

A 53-year-old man with systemic lupus erythematosus for which he was being treated with 1 mg/day prednisone for 20 years presented with a 1-month history of right eye swelling. His primary care physician initially treated him for sinusitis, but his condition worsened and he developed double vision. CT showed a right ethmoid, sphenoid, and frontal sinus mass that extended into the medial aspect of the right orbit. He was referred to an otolaryngologist who performed a transnasal endoscopic biopsy.

Before the biopsy, the patient had been evaluated in the Neuro-Ophthalmology/Orbital Division of the Wilmer Eye Institute, The Johns Hopkins Hospital, at which time he had a best-corrected visual acuity of 20/20 in both eyes, normal color vision, and normal visual fields in both eyes. The pupils were isocoric, and the pupillary responses were normal. The right eye showed mild limitation of supraduction. The left eye had full ductions. The patient was orthophoric in primary gaze but developed a 4 prism diopter (PD) left hypertropia in upgaze and an esotropia of 5 PD on downgaze. There was 2 mm of proptosis of the right eye. The patient was given 20 mg/day prednisone with improvement in right eye swelling and diplopia.

At biopsy, the sinuses were filled with mucus, and there was no evidence of infection. The orbit was therefore entered, at which time a firm mass was encountered. Biopsy of the lesion showed chronic inflammation; immunophenotyping showed a mixed process including both B and T cells (Fig. 1). No cellular atypia was present. A diagnosis of idiopathic sino-orbital inflammation was made, and the prednisone dose was increased to 40 mg/day. Within 4 weeks, the patient's symptoms and signs had resolved completely, and CT showed complete resolution of the sino-orbital lesion.

A slow taper of his prednisone dose was initiated, whereupon his symptoms and signs recurred, and CT showed recurrence of the lesion. Accordingly, low-dose fractionated radiation therapy was recommended. The patient elected to delay radiation treatment, and his prednisone dose was increased to 20 mg/day. Despite this treatment, during the next 2 months he developed right upper eyelid swelling, right ptosis, and a severe headache. CT now showed intracranial extension of the mass, and MRI showed a right orbital lesion that measured 2.2 × 0.9 × 3.0 cm extending intracranially through a dehiscent cribriform plate with intraparenchymal involvement of the right frontal lobe and surrounding edema with focal areas suggestive of either necrosis or abscess formation (Fig. 2). Leptomeningeal enhancement of the subarachnoid portion of the right third cranial nerve was also visible.

A neuro-ophthalmological examination now revealed a best-corrected visual acuity of 20/60 in the right eye and 20/20 in the left eye. The right pupil was 2 mm larger than the left and unreactive to direct light. There was no relative afferent pupillary defect. The patient had a complete right ptosis. The right eye showed absentsupraduction, infrafduction, and adduction but intact abduction and intorsion attempted downgaze. There was a right exotropia of 60 PD and a small left hypertropia in primary gaze position, findings all consistent with a complete third cranial nerve palsy (Fig. 3). A firm, nontender mass was palpable in the superomedial orbit. Slit-lamp biomicroscopic examination and ophthalmoscopy revealed no abnormalities.

A transcutaneous trans-septal orbital biopsy showed friable fibrous tissue containing an inflammatory infiltrate with numerous large, irregular cells featuring vacuolated cytoplasm and heterochromatic nuclei. The Ki67 proliferation index was more than 25%. Results of immunostaining were positive for CD56 as well as for cytoplasmic CD3, CD4, CD7, CD43, and the cytoplastic granule protein T-cell intracellular antigen-1 (TIA-1) (Fig. 4). Results of immunostains for CD5 and CD8 and Epstein-Barr virus (EBV) latent membrane protein (LMP)-1 were negative. In situ hybridization also failed to detect EBV.

Systemic evaluation revealed two pulmonary masses in the right upper lobe. Lumbar puncture showed a mixed pleocytosis with polymorphonuclear leukocytes and monocytes and protein of 87 mg/dL (normal 15–45 mg/dL). No tumor cells were detected in the cerebrospinal fluid, but...
flow cytometry of the fluid showed mainly T cells. Spine MRI was normal. Bone marrow biopsy was negative for tumor, but positron emission tomographic scanning showed intense activity in the chest. A diagnosis of metastatic NKTL was made.

The patient was treated with intrathecal cytarabine, intravenous doxorubicin, vincristine, and cyclophosphamide, and oral allopurinol as well as whole-brain irradiation. His condition improved initially, but he died 13 months after the onset of symptoms and signs.
**DISCUSSION**

NKTL is a predominantly extranodal malignancy most commonly positive for EBV and CD56, reflecting a natural killer (NK) cell phenotype, with occasional patients lacking CD56 expression (cytotoxic T-cell phenotype) (2). This tumor is thought to derive from the malignant transformation of mature NK cells or post-thymic T cells (4). It comprises 1% of all lymphomas in patients of European descent, although the incidence is higher in Asian, South American, and Hispanic peoples (5).

NKTL usually is located in the nasal cavity or paranasal sinuses, in which it was previously called idiopathic midline destructive lesion, angiocentric lymphoma, or, in cases in which the angiocentrically oriented cells appeared to form granulomas, malignant midline granuloma or lethal midline granuloma-NKTL (6,7). Ophthalmic involvement is reported infrequently. For example, Davison et al (8), reported 30 cases of nasal NKTL without orbital involvement, and Cuadra-Garcia et al (9) found only one case of orbital involvement among 17 cases of NKTL. Because of the location of most NKTLs, the ophthalmic manifestations usually arise from direct infiltration of orbital structures or associated orbital inflammation and include proptosis, conjunctival chemosis, and restriction of eye movements (10). Other ophthalmic manifestations of NKTL include vision loss from optic nerve dysfunction, rhegmatogenous retinal detachment, and uveitis (11,12).

Neurologic deficits are rare in patients with NKTL. Luther et al (3) reported that fewer than 3% of cases of nasal NKTL were associated with intracranial involvement. When intracranial extension does occur, the process usually is characterized by an abscess-like appearance on neuroimaging as seen in our patient. This appearance is caused
by the angiocentric growth pattern and surrounding destruction, resulting in zonal necrosis.

Neuro-ophthalmologic manifestations of NKTL are also rare. Hon et al (12) reported a case of NKTL that produced unilateral ophthalmoplegia from combined third, fourth, and sixth cranial nerve palsies. We believe our patient is the first in whom an isolated third cranial nerve palsy was caused by intracranial extension of an NKTL. In our patient, the subarachnoid and cavernous portions of the nerve showed enhancement on MRI, suggesting either infiltration by the tumor or a local inflammatory response.

The diagnosis of NKTL is difficult in its early stages for several reasons. First, NKTL has a broad cytologic spectrum. The atypical cells may be small or medium-sized, large and hyperchromatic, or a mixture of these cell types. If small and medium-sized cells predominate, the disease may be difficult to distinguish from an inflammatory or infectious process (13) as occurred in our patient. Second, NK cells may produce a variety of cytokines such as interferon-α and tumor necrosis factor-α that modulate the adaptive portion of the immune response and recruit a prominent mixture of inflammatory cells, causing further difficulty in differentiating NKTL from admixed or adjacent nonspecific chronic inflammation (11). Third, in the early stages of the disease, relatively few neoplastic cells are present, and the NK cells that are present are usually located angiocentrically with areas of surrounding necrosis (14). Thus, biopsy of these lesions may not include the neoplastic cells. Because of these issues, multiple or extensive biopsies are often required to obtain sufficient viable tissue (14).

Evidence of EBV infection is detected in 80% of cases of NKTL and is associated with a shorter survival and a more advanced clinical stage than is NKTL without EBV infection (15). In addition, NKTLs commonly express cytotoxic granule proteins such as TIA-1, perforin, and Fas ligand, all of which are important mediators of tissue damage (16). The marker CD56 almost always is present in NK cells as well as in some T cells, and CD3 is found in the cytoplasm of both NK cells and T cells (2,5). In our case, neither EBV nuclei acid nor EBV LMP was detected in the second biopsy specimen; however, the cells expressed both CD56 and TIA-1. An unusual feature of this case was the expression of CD4, which is present in 10% or fewer NKTLs (17).

Because of the rarity of NKTL, treatment recommendations are based primarily on the results of prospective cohort reports. Localized nasal NKTL is usually sensitive to radiation therapy (11), but failure to achieve a complete response and early relapse are common problems (4). Once dissemination to the orbit or intracranial space occurs, as in this patient, long-term remission, even with aggressive chemotherapy, is rare. Overall outcome is poor, with a 5-year survival rate of 26% and a reported disease-free survival of 20% (18). Most patients die of their disease within 1–2 years.

REFERENCES
Isolated Lymphoma of the Anterior Visual Pathway Diagnosed by Optic Nerve Biopsy

Joseph R. Zelefsky, MD, Carolyn H. Revercomb, MD, George Lantos, MD, and Floyd A. Warren, MD

Abstract: A 72-year-old previously healthy man developed rapidly progressive visual loss, and brain imaging showed features suggestive of a malignant glioma of the anterior visual pathway. Biopsy of one optic nerve yielded a diagnosis of lymphoma. There was no evidence of an extracranial non-Hodgkin lymphoma, so the conclusion was that this represented a primary central nervous system lymphoma (PCNSL). PCNSL isolated to the optic chiasm has been described only once in an immunocompetent patient. Our patient is unusual in that the lymphoma involved the optic nerve, chiasm, and tract in an immunocompetent patient.

CASE REPORT

A 72-year-old man was referred to the neuro-ophthalmology clinic for progressive painless loss of vision in the right eye for 6 weeks. His past medical history was significant for hypertension and newly diagnosed diabetes mellitus. He denied headache, weight loss, or other constitutional symptoms.

Best-corrected visual acuity was count fingers at 1 foot in the right eye and 20/25 in the left eye. Confrontation visual field testing was suggestive of an inferior altitudinal defect in the right eye and was full in the left eye. Ishihara

FIG. 1. Humphrey visual field of the left eye demonstrates a dense temporal hemianopia.
color vision testing was normal in the left eye. There was an afferent pupillary defect in the right eye. On slit lamp examination, the anterior segments of both eyes were unremarkable. Dilated funduscopic examination demonstrated pallor of the right optic disc and a normal-appearing left optic disc. The vitreous was clear, and the retina and choroid were normal in both eyes.

Results for a complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), angiotensin-converting enzyme (ACE), rapid plasma reagin (RPR), microhemagglutination-Treponema pallidum (MHA-TP), and Lyme titer (enzyme-linked immunosorbent assay [ELISA]) were within normal limits. C-reactive protein was elevated at 4.83 mg/dL (normal < 1 mg/dL). The patient returned a few days later, reporting that the vision in his left eye was worsening. Automated visual field testing demonstrated a dense temporal hemianopic defect in that eye (Fig. 1).

Brain MRI (Figs. 2 and 3) showed abnormal contrast enhancement of the intracranial portion of the right optic nerve and optic chiasm. Contrast enhancement extended posteriorly to the right optic tract and toward the left lateral geniculate body. Of interest, the enhancement of the lesion demonstrated a “layered” appearance, reminiscent of the histologic organization of the lateral geniculate nucleus.

Given the imaging findings and the poor vision in the right eye, the patient underwent transcranial biopsy of the right optic nerve. Microscopic examination (Fig. 4) revealed a tumor composed of closely packed cells with frequent mitotic figures. Immunohistochemical staining revealed that most cells had membranous positivity for the B-cell antigen CD20. The tumor cells were also positive for bel-2, but negative for CD5, CD10, and bel-1. An MIB-1 immunostain, which labels the Ki-67 proliferation-associated antigen, labeled more than 50% of the large tumor cells. Admixed small T lymphocytes were marked by
antibodies to the T-cell antigens CD3 and MT-1 (CD43). The light microscopic appearance and immunohistochemical profile established the diagnosis of non-Hodgkin lymphoma of diffuse small B-cell type. The immunophenotype was consistent with origin from follicular center cells.

CT scans of the chest, abdomen, and pelvis did not show any evidence of systemic lymphoma or other medical conditions. Further tests with normal results included a CBC with differential, a complete metabolic panel, and an HIV titer. Treatment with high-dose methotrexate, leucovorin, and prednisone was initiated. Over the next few weeks, the patient’s condition deteriorated and he died 3 months later.

DISCUSSION

Lymphomatous involvement of the optic nerve most often occurs as a result of metastatic spread of systemic
Lymphoma of the Anterior Visual Pathway

NHL (3). PCNSL of the optic nerve is rare, and isolated PCNSL involvement of the anterior visual pathway is even rarer. There have been scant case reports of optic nerve involvement in patients with NHL (1-6). PCNSL infiltration of the optic nerve and chiasm has been reported in patients with AIDS (2,7), in whom the incidence of PCNSL is increased (8-11). Gray et al (12) reported a patient with headaches, loss of hearing, and loss of vision, who had a PCNSL of the optic chiasm. To our knowledge, our case is unusual in that PCNSL involved the optic nerve, chiasm, and tract in an otherwise asymptomatic patient without AIDS or other systemic immunosuppressed state.

Although the histopathologic characteristics of PCNSL and NHL metastatic to the intracranial space are practically indistinguishable, PCNSL most often involves the brain parenchyma, typically near the ventricles, whereas NHL with secondary central nervous system (CNS) involvement usually presents in the leptomeninges or dura (13). The lack of dural or meningeal involvement in our patient, together with the absence of any extracranial manifestations of NHL noted on his systemic workup, suggests that his lymphoma falls into the category of PCNSL.

In our patient, the relatively rapid and progressive visual loss in both eyes in a previously healthy older man, coupled with the imaging abnormalities, suggested malignant glioma of the optic nerve and chiasm. This case demonstrates the importance of considering the diagnosis of lymphoma in this setting.

REFERENCES
Multiple Intracranial Meningiomas Causing Papilledema and Visual Loss in a Patient With Nevoid Basal Cell Carcinoma Syndrome

Jonathan T. Pribila, MD, PhD, Shawn M. Ronan, MD, and Jonathan D. Trobe, MD

Abstract: A 27-year-old man with nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome) who had undergone craniospinal irradiation for a childhood brain stem medulloblastoma complained of progressive binocular visual loss. Ophthalmologic examination disclosed subnormal visual acuity and visual fields in both eyes attributed to chronic papilledema. Brain MRI demonstrated mass effect from multiple large meningiomas. After embolization and surgical resection of the largest meningioma, papilledema disappeared and visual dysfunction resolved partially. This is the sixth reported patient with NBCCS, medulloblastoma, and craniospinal radiation who has developed intracranial meningioma, further documenting the fact that such patients have a relatively high likelihood of developing meningiomas, especially multiple meningiomas. Because patients with NBCCS are often mentally impaired and because papilledema can progress silently before causing irreversible visual loss, periodic ophthalmologic examination is advisable after craniospinal radiation.


Nevvoid basal cell carcinoma syndrome (NBCCS), also called basal cell nevus syndrome, Gorlin syndrome, and Gorlin-Goltz syndrome, is a rare autosomal dominant disorder with a prevalence of 1 in 57,000–164,000 (1–3). It is characterized by early basal cell carcinomas, craniofacial abnormalities (odontogenic keratocysts, macrocephaly, frontal bossing, cleft lip or palate, hypertelorism, and calcification of the falx cerebri) and skeletal anomalies (bifid, fused, or splayed ribs, pectus deformity, and syndactyly of digits) (4,5).

Medulloblastoma occurs in approximately 3%–5% of patients with NBCCS with a 3:1 male gender predilection (6). In the general population, medulloblastoma presents at age 7–8 years, whereas in NBCCS it presents at age 1–2 years (1,4). Surgical resection and craniospinal radiation are standards in the postoperative care of patients with medulloblastoma. There have been several reports of meningiomas in patients with NBCCS after craniospinal radiation (4,7–10), but the relationship between the development of these tumors and previous exposure to craniospinal radiation has not been reviewed in detail.

We report a patient with NBCCS who developed multiple intracranial meningiomas decades after having had resection of a medulloblastoma and postoperative craniospinal radiation. The meningiomas produced increased intracranial pressure that went unrecognized until he complained of worsening vision caused by chronic papilledema.

CASE REPORT

A 27-year-old man with known NBCCS presented to an optometrist with the gradual development of blurred vision in both eyes over several months. The patient was found to have bilateral optic nerve edema and was referred to an emergency room.

He also described worsening headaches accompanied occasionally by nausea and vomiting over the previous month. The patient's family reported a slow mental decline over the previous several years marked by difficulty in word finding and following simple instructions. An avid reader of Shakespeare, he had stopped this 2 months earlier. He denied neck pain, difficulty with coordination, and focal numbness and weakness.

A brain stem medulloblastoma had been resected at age 17 months and treated with craniospinal radiation.
He had not had regular medical care since age 5. His mother reported that she also had NBCCS. At the time of presentation, the patient had become unemployed and was living with his parents. Multiple basal cell nevi were present on the head and trunk. He was alert, fully oriented, and able to perform simple calculations. Repetition and naming were intact, but he had difficulty with word finding and following complex commands. The rest of the neurologic examination was normal except for visual function.

Best-corrected visual acuity was 20/60 in both eyes. An afferent pupillary defect was present in the right eye. Results of slit lamp examination were unremarkable. Fundus examination revealed bilateral optic disc edema (Fig. 1). Visual fields, performed on the Humphrey perimeter, showed mean deviations of 10.21 dB in the right eye and 6.11 dB in the left eye with nerve fiber bundle loss in both eyes (Fig. 2).

Brain MRI demonstrated ventriculomegaly and six intracranial but extra-axial enhancing masses (Fig. 3). The largest mass was in the left temporoparietal region. It measured 7.2 by 5.7 cm and compressed the lateral ventricle and brain stem. There were also two masses in the right frontal lobe, two in the left frontal lobe, and one in the right temporal lobe. Calcification was seen throughout the tentorium and falx cerebri.

The patient underwent embolization and surgical resection of the left temporoparietal meningioma. Histologic analysis revealed a grade 1 transitional, microcystic, and fibrous meningioma with a proliferation index range from 0% to 5%–10% in MIB-1 stained sections.

Three months after resection of the meningioma, the patient’s best-corrected visual acuity was 20/30 in the right eye and 20/20 in the left eye. The optic disc edema had disappeared (Fig. 4), but the afferent pupillary defect in the right eye persisted. Repeat Humphrey visual field perimetry demonstrated an improvement in visual fields with mean deviations of 6.9 dB in the right eye and 4.4 dB in the left eye (Fig. 5). MRI demonstrated that the tumor mass effect had disappeared (Fig. 6).

The patient has since undergone excision of the remaining tumors and had no neurologic setbacks. Histopathologic examination showed all tumors to be meningiomas.

DISCUSSION

We have described a patient with NBCCS who, after having received craniospinal radiation for a medulloblastoma as a child, developed multiple large meningiomas causing an intracranial mass effect that led to the
FIG. 3. Postcontrast T1 axial brain MRI performed at presentation. The left temporoparietal meningioma (A-C) exerts mass effect on the lateral ventricle and brain stem. There are also masses in the right temporal lobe (B-C), right frontal lobe (C), and left frontal lobe (D).

Twelve other patients with NBCCS who developed meningiomas have been reported (Table 1). Six patients, including ours, had undergone craniospinal radiation for medulloblastoma between age 15 and 34 years before

FIG. 4. Fundus photographs obtained 3 months after resection of the temporoparietal meningioma demonstrate resolution of papilledema.

development of chronic papilledema and consequent visual acuity and visual field loss. The patient’s complaint of blurred vision brought the meningiomas to medical attention.
FIG. 5. Humphrey perimetry performed 3 months after surgical resection of the temporoparietal meningioma shows improvement relative to the preoperative visual fields with mean deviations of $-6.9$ dB in the right eye and $-4.4$ dB in the left eye.

the diagnosis of meningioma (4,7-10). Six patients had received no radiation, and one patient had received low-dose external radiation for basal cell carcinoma (11). The six patients who had received craniospinal radiation had a higher incidence of development of multiple meningiomas than the seven patients who had not received such radiation. Five (83%) of the six patients who received radiation developed multiple meningiomas. In comparison, of the seven patients who had not received craniospinal irradiation, only one (8.3%) developed multiple meningiomas. One of these patients also developed a left temporal fossa schwannoma and a liposarcoma of the scalp.

The development of meningiomas after craniospinal radiation in patients without NBCCS appears to be less common than in those with NBCCS (17,18). In a review of 77 reports of patients who developed meningiomas after high-dose craniospinal radiation, Musa et al (17) estimated the overall frequency of meningioma to be 3.5%. In that review, 6 patients (7.9%) had multiple meningiomas (17).

The biochemical basis for NBCCS provides some insight into a potential molecular mechanism for the proclivity to develop second tumors. The NBCCS gene PTCH has been mapped to chromosome 9q22.3 and encodes Patched, a transmembrane receptor critical to sonic hedgehog-mediated cell cycle control through its inhibition of downstream modulators such as Smoothened (3,19-21). In patients with NBCCS, one allele produces a non-functional protein, leaving the cell sensitive to a “second hit” that would disrupt the other allele and render the cell resistant to sonic hedgehog-mediated regulation of the cell cycle. Craniospinal radiation would probably provide the mutagenic force necessary to cause this second hit and allow for unregulated cell growth and tumor formation.

Although craniospinal irradiation is a mainstay of treatment for medulloblastomas, it should be acknowledged that patients with NBCCS develop multiple meningiomas at a much higher frequency than the general population after craniospinal irradiation. These tumors may cause increased intracranial pressure by mass effect or blockage of cerebrospinal fluid egress. When intracranial pressure increases slowly, an important adverse consequence is chronic papilledema and optic nerve damage. Periodic ophthalmologic examination, especially of the optic fundus, is recommended in these patients for two reasons: 1) they may be mentally impaired and unaware or unable to articulate visual problems; and 2) papilledema may progress for a long time before causing visual loss, at which time the visual loss may be irreversible.

FIG. 6. Postcontrast T1 axial brain MRI performed 3 months after surgical resection of the temporoparietal meningioma shows resolution of the mass effect. A-D are comparable in level to those of Fig. 3.
### TABLE 1. Reported cases of meningiomas in patients with nevoid basal cell carcinoma syndrome

<table>
<thead>
<tr>
<th>Patient (Ref.)</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Number and location of tumor(s)</th>
<th>Initial symptom</th>
<th>Craniospinal radiation (years to presentation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (12)</td>
<td>64</td>
<td>M</td>
<td>1 meningioma1 craniopharyngioma  (location not described)</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>2 (13)</td>
<td>60</td>
<td>M</td>
<td>olfactory meningioma</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>3 (14)</td>
<td>18</td>
<td>F</td>
<td>Multiple meningiomas            (location not described)</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>4 (11)</td>
<td>47</td>
<td>F</td>
<td>1 right frontoparietal meningioma</td>
<td>Hemiparesis and seizures</td>
<td>No</td>
</tr>
<tr>
<td>5 (15)</td>
<td>60</td>
<td>M</td>
<td>1 left temporal fossa meningioma</td>
<td>Sixth cranial nerve palsy and decreased vision</td>
<td>No</td>
</tr>
<tr>
<td>6 (16)</td>
<td>24</td>
<td>F</td>
<td>1 left temporoparietal meningioma</td>
<td>Ventricular fibrillation</td>
<td>No</td>
</tr>
<tr>
<td>7 (11)</td>
<td>44</td>
<td>M</td>
<td>1 left parietal lobe meningioma</td>
<td>Aphasia and dysarthria; weakness and numbness of the right hand</td>
<td>No*</td>
</tr>
<tr>
<td>8 (4)</td>
<td>26</td>
<td>M</td>
<td>Multiple meningiomas with brain stem compression</td>
<td>Neurologic symptoms (not described)</td>
<td>Yes (22)</td>
</tr>
<tr>
<td>9 (7)</td>
<td>19</td>
<td>F</td>
<td>1 frontal lobe meningioma with extracranial extension</td>
<td>Forehead mass</td>
<td>Yes (15)</td>
</tr>
<tr>
<td>10 (10)</td>
<td>28</td>
<td>M</td>
<td>1 right temporal fossa meningioma1 right temporal fossa meningioma1 left temporal fossa schwannoma1 liposarcoma of the scalp</td>
<td>Depression</td>
<td>Yes (26)</td>
</tr>
<tr>
<td>11 (9)</td>
<td>35</td>
<td>M</td>
<td>1 tuberculum sellae meningioma3 parasellar meningiomas</td>
<td>Visual field defects and visual loss</td>
<td>Yes (34)</td>
</tr>
<tr>
<td>12 (8)</td>
<td>19</td>
<td>F</td>
<td>1 left parietal lobe meningioma1 right parietal lobe meningioma</td>
<td>Change in affect</td>
<td>Yes (17)</td>
</tr>
<tr>
<td>13 (present case)</td>
<td>27</td>
<td>M</td>
<td>1 left temporoparietal lobe meningioma1 right temporal lobe meningioma2 left frontal lobe meningiomas</td>
<td>Blurred vision</td>
<td>Yes (25)</td>
</tr>
</tbody>
</table>

NA, not applicable.
*Received external radiation to the scalp.

### REFERENCES


Orbital Metastasis of Hepatocellular Carcinoma

Parima Hirunwiwatkul, MD, Suppapong Tirakunwichcha, MD, Piyawadee Meesuaypong, MD, and Shanop Shuangshoti, MD

Abstract: We report a 74-year-old woman who presented with an orbital apex syndrome and pulsatile proptosis. CT showed a right orbital mass that destroyed the orbital sphenoid bone and extended intracranially. Biopsy revealed metastatic hepatocellular carcinoma (HCC), and subsequent investigations demonstrated a high level of serum-fetoprotein and a huge liver mass. The patient died shortly after the biopsy. Rarely reported in the English literature, metastatic HCC is common in Asia, perhaps because of a racial predisposition together with a relatively high prevalence of alcoholic cirrhosis, chronic hepatitis B and C, and exposure to aflatoxins.


Metastatic tumor accounts for 3%-7% of orbital neoplasms (1) and the common primary sources of tumor are carcinoma of the breast and lung. Hepatocellular carcinoma (HCC) usually metastasizes to the lung, lymph nodes, adrenal gland, and bone. Orbital metastasis of HCC is rare, with only 14 biopsy-proven cases reported in the English literature (2–15).

Common presenting symptoms of orbital metastasis of HCC include pain, proptosis, and visual loss (2–15). Most patients have been in an advanced stage of cancer and have typically died within 1 year of diagnosis. The purpose of this article is to report a case of orbital metastasis of HCC that caused an orbital apex syndrome and pulsatile proptosis.

CASE REPORT

A 74-year-old woman complained of headache and pain around the right eye for 2 months. She used antimigraine drugs that alleviated the pain. She denied proptosis and double vision. An ophthalmologist diagnosed glaucoma and cataract. Anti-glaucomatous drugs were dispensed. Her past medical history included diabetes mellitus, ischemic heart disease, and essential hypertension for 6 years. Her son and daughter had renal failure of unknown cause. She lived alone and had consumed alcohol heavily for 10 years.

One week before her visit to us, she developed severe right-sided headache, rapidly progressive proptosis, deterioration of vision, and ptosis of the right eye. She reported a 7-kg weight loss within the past month.

Ophthalmologic examination elsewhere disclosed intraocular pressures of 31 mm Hg in the right eye and 27 mmHg in the left eye, a right afferent papillary defect, as well as proptosis (Fig. 1) and reduced eye movements of the right eye in all directions. CT of the orbit showed a right orbital mass presumptively diagnosed as rhabdomyosarcoma (Fig. 2).

On our examination, visual acuity was hand movements in the right eye and finger counting in the left eye. Spontaneous pulsatile right proptosis and ptosis were observed on the right. She had orthophoria in primary position but the right eye had only 15% abduction and supraduction and 20% adduction and infraduction. The left eye...
eye moved normally. The right pupil was dilated, with an afferent pupillary defect. Slit lamp examination revealed dense cataracts bilaterally, which precluded a view of the optic fundus. Decreased sensation was found on the right cornea and on the right side of face. There were no other neurologic deficits or lymphadenopathy detected.

Orbital CT showed an 8 by 9 cm lobulated, hyperdense, and uniformly-enhancing mass in the superolateral portion of the right orbit. The lesion extended into the anterior portion of the middle cranial fossa with bony destruction. Results of a complete blood count and standard blood chemistry analyses were within normal ranges except for elevated levels of serum glutamic oxaloacetic transaminase (SGOT) (115 U/L) and total bilirubin (1.57 mg/dL).

Biopsy of the orbital mass revealed polygonal-shaped tumor cells with vesicular nuclei and prominent nucleoli (Fig. 3). The cells formed trabeculae rimmed by flat endothelium. Mitoses were occasionally encountered. Tumor cells stained positively with cytokeratin AE1/AE3, HepPar-1, and alpha-fetoprotein (AFP). A pathologic diagnosis of metastatic HCC was rendered.

Subsequent CT of the abdomen revealed a huge liver mass with retroperitoneal lymphadenopathy. The serum AFP level was markedly elevated (12,164 ng/mL). These
findings further supported the diagnosis of HCC. Results of viral hepatitis profiles were negative. The patient received palliative treatment and died 2 months later.

**DISCUSSION**

Only 14 biopsy-proven cases of orbital metastasis of HCC have been reported in the English literature (Table 1). No cases have been reported in large series from the United States and Europe (1, 16, 17), but in Japan, HCC ranks as the third most common cause of orbital metastatic cancers (18). This significant difference in orbital metastatic HCC is most likely due to the higher incidence of HCC in Asia. The incidence of HCC exceeds 30 in 100,000 in East Asia (19) and ranges between 1.2 and 8.8 in 100,000 in the United States (20) and 3 and 12 in 100,000 in Europe (21).

Several risk factors for HCC development are frequently encountered in tropical Asian areas, particularly alcoholic cirrhosis (22), chronic hepatitis B and C (23–25), and exposure to aflatoxins (26), carcinogens produced by *Aspergillus*. Infection with hepatitis B virus is the major risk factor for HCC in Thailand, with an estimated relative risk of 15.2 (27).

There have been many reports of an association between these risk factors and genetic abnormalities (28, 29). Cai et al (30) have shown autosomal recessive inheritance of a major gene that influences the age of onset of HCC in eastern China. There have also been various studies dealing with the genetic predisposition to HCC among alcoholics. The alcohol dehydrogenase 1C*1 allele has been found to be a genetic marker for alcohol-associated cancer in heavy drinkers (31). The presence of at least one alanine manganese superoxide dismutase (Ala-MnSOD) allele increased the risk of development of cirrhosis in French alcoholics and increased the rate of

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Sex</th>
<th>Nationality</th>
<th>Location of Metastasis</th>
<th>Associated Risk</th>
<th>Presenting Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubin et al (2)</td>
<td>69/M</td>
<td>American</td>
<td>Superoposterior orbit</td>
<td>Cirrhosis, alcoholism</td>
<td>Progressive proptosis</td>
</tr>
<tr>
<td>Zubler et al (3)</td>
<td>64/M</td>
<td>American</td>
<td>Lateral aspect</td>
<td>Alcoholism</td>
<td>Proptosis, ophthalmoplegia</td>
</tr>
<tr>
<td>Wakisaka et al (4)</td>
<td>58/M</td>
<td>Japanese</td>
<td>Frontal base extending to intraorbital space</td>
<td>HBV infection</td>
<td>Pain and ophthalmoplegia</td>
</tr>
<tr>
<td>Phanthumchinda and Hemachuda (5)</td>
<td>29/W</td>
<td>Thai</td>
<td>Superior orbital fissure</td>
<td>HBV infection</td>
<td>Pain and proptosis</td>
</tr>
<tr>
<td>Tranfa et al (6)</td>
<td>85/M</td>
<td>Italian</td>
<td>Superotemporal orbit</td>
<td>N/A</td>
<td>Proptosis with exposure keratitis</td>
</tr>
<tr>
<td>Schwab et al (7)</td>
<td>19/M</td>
<td>African</td>
<td>Superior orbit</td>
<td>N/A</td>
<td>Progressive visual loss</td>
</tr>
<tr>
<td>Loo et al (8)</td>
<td>71/W</td>
<td>Chinese</td>
<td>Anterior cranial fossa extending into orbit</td>
<td>HBV infection</td>
<td>Headache with visual disturbance</td>
</tr>
<tr>
<td>Hosakawa et al (9)</td>
<td>70/M</td>
<td>Japanese</td>
<td>Lateral orbital wall</td>
<td>N/A</td>
<td>Proptosis and visual loss</td>
</tr>
<tr>
<td>Font et al(10)</td>
<td>79/W</td>
<td>Mexican</td>
<td>Posterolateral orbital wall</td>
<td>HCV infection</td>
<td>Periorbital mass</td>
</tr>
<tr>
<td>Scolyer et al (11)</td>
<td>78/M</td>
<td>Australian</td>
<td>N/A</td>
<td>N/A</td>
<td>Inferior displacement of eye</td>
</tr>
<tr>
<td>Kim et al (12)</td>
<td>56/W</td>
<td>Korean</td>
<td>Lateral orbital wall</td>
<td>HBV infection</td>
<td>Proptosis</td>
</tr>
<tr>
<td>Gupta et al (13)</td>
<td>45/M</td>
<td>Indian</td>
<td>Superotemporal orbit</td>
<td>HBV infection</td>
<td>Proptosis</td>
</tr>
<tr>
<td>Machado-Netto et al (14)</td>
<td>57/M</td>
<td>Brazilian</td>
<td>Temporal aspect of orbit</td>
<td>HBV infection</td>
<td>Proptosis</td>
</tr>
<tr>
<td>Oida et al (15)</td>
<td>72/M</td>
<td>Georgian</td>
<td>Superolateral orbit</td>
<td>HCV infection</td>
<td>Diplopia, pain, proptosis</td>
</tr>
</tbody>
</table>

M, male; F, female; N/A, not available; HBV, hepatitis B virus; HCV, hepatitis C virus.
HCC development and death in cirrhotic patients (32). Alterations in genes involved in the RB1 and p53 pathways have been implicated in alcohol-related tumors (33).

HCC can metastasize indirectly to the orbit via the skull base or directly to orbital tissue. The most common metastatic site within the orbit is the superotemporal region. Pain, proptosis, and visual loss are the typical presenting manifestations (5) (Table 1). Bone destruction is common. Delayed diagnosis in our patient presumably allowed the mass to destroy the bone of the posterior orbit and create pulsatile proptosis, a manifestation not previously described.

REFERENCES

Homonymous Hemianopia Caused by Solitary Skull Metastasis of Hepatocellular Carcinoma

Sheng-Yao Hsu, MD, Fang-Ling Chang, MD, Min-Muh Sheu, MD, and Rong-Kung Tsai, MD

FIG. 1. A. Preoperative brain MRI shows a mass in the left parietooccipital cranium (arrow) with osteolytic change and compression of the left posterior ventricular horn and left cerebral sulci on a precontrast T1 study. B. The postcontrast study shows avid enhancement of the mass. C. Catheter angiography shows tumor supply by the left occipital and posterior branches of the left superficial temporal artery (arrow). D. Preoperative Humphrey visual fields show a complete right homonymous hemianopia.

Department of Ophthalmology (S-YH, F-LC, M-MS, R-KT), Buddhist Tzu Chi General Hospital, Hualien, Taiwan; Institute of Medical Sciences and Medicine (S-YH), College of Medicine, Tzu Chi University, Hualien, Taiwan; and Institute of Medicine (M-MS, R-KT), College of Medicine, Tzu Chi University, Hualien, Taiwan.

S.-Y.H. and F.-L.C. contributed equally to this work.

Address correspondence to Rong-Kung Tsai, MD, Department of Ophthalmology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chungyang Road, Hualien, Taiwan; E-mail: wps59@yahoo.com.tw
Abstract: We report a patient who developed a complete left homonymous hemianopia from mass effect of a solitary skull metastasis of hepatocellular carcinoma (HCC). After chemoembolization and resection, the visual field defect improved markedly. This is the first reported case demonstrating this phenomenon in HCC. It supports aggressive treatment of a solitary skull metastasis in this setting.


A 53-year-old man complained of blurred vision in his right visual field for the past 2 months. He had noted a protruding bump over his left parieto-occipital area for 4 months.

The patient had a long history of type 2 diabetes mellitus, alcoholism with cirrhosis, and hepatitis B virus infection. Tea-colored urine with occasional tarry stools had been noted for more than 1 year. Seven months earlier, hepatocellular carcinoma (HCC) had been diagnosed, and he had received transarterial chemoembolization. Abdominal sonography had disclosed the tumor and cirrhosis, splenomegaly, and gallstones.

Best-corrected visual acuities were 20/20, and results of all other aspects of our examination were normal except for Humphrey automatic perimetry, which showed complete right homonymous hemianopia (Fig. 1).

Brain MRI showed a mass in the left parieto-occipital calvarium with osteolytic change and compression of the left posterior ventricular horn and left cerebral sulci with midline shift to the right. The cerebral parenchyma showed normal signal intensity without brain metastasis (Fig. 1). Chest and abdominal CT, including visualization of vertebrae, showed no abnormalities. We concluded that the patient had developed a solitary metastasis of HCC to the skull.

Cerebral angiography showed a large hypervascular tumor stain and venous aneurysms in the left parieto-occipital bone supplied by the left occipital and posterior branches of the left superficial temporal artery, findings compatible with a solitary skull metastasis (Fig. 1).

Selective transarterial embolization of the feeding arteries was performed via coaxial microcatheter systems with 300–500 μm microspheres and four metallic microcoils. After the chemoembolization, angiography revealed 80% reduction in vascularity. On the following day, left parieto-occipital craniectomy revealed a large epidural and subgaleal mass with skull bone erosion and intact dura. The pathologic study showed HCC (Fig. 2).

One month postoperatively, head CT showed less compression of the left posterior ventricular horn and less effacement of the left cerebral sulci with residual cranial osteolytic change and epidural effusion (Fig. 3). The dura remained intact and free of metastasis. Repeat perimetry showed visual field improvement (Fig. 3). Results of the ophthalmologic examination remained normal.

The patient later received 28 fractions of 180 cGy for a total of 5,040 cGy of whole brain x-irradiation. During a follow-up of 9 months, he remained free of known recurrence of HCC or any complications of treatment.

The highest annual incidence rates of HCC, approaching 150 per 100,000, are found in Taiwan, Korea, Mozambique, and Southeast China and are strongly linked to the prevalence of hepatitis B infection (1). In Taiwan, HCC is the leading cause of death by malignant neoplasm in men. In China, the lifetime risk of developing HCC in patients with chronic hepatitis B approaches 40% (2).

FIG. 2. Pathologic examination of the extirpated mass. A. The gross specimen is greenish-brown in color and soft with focal necrosis (arrow). B. Part of the skull bone (arrow) is invaded by the tumor. C. Histopathologic examination reveals a trabecular pattern and bile production (arrow) (hematoxylin-eosin stain; original magnification ×400).
Hepatocellular Carcinoma


FIG. 3. A–C. One month after removal of the skull tumor, head CT shows markedly reduced mass effect, residual cranial osteolytic change, and epidural effusion (arrow). D. Humphrey visual fields show visual field improvement.

We believe that our description of a solitary skull metastasis of HCC in a Taiwanese man represents the first report of this phenomenon. Although HCC is a relatively more common malignant tumor in Taiwan than in non-Asian areas, HCC skull metastasis is still a relatively rare condition, even in Taiwan.

The incidence of HCC is increasing, not only in Asia but also in the United States, perhaps because of an increase in the rate of detection of viral hepatitis (3). HCC is four times more common in men than in women and usually arises in a cirrhotic liver (4). It commonly metastasizes to the lung, regional lymph nodes, peritoneum, adrenal glands, and bone (5–7), the most common bony site being the vertebra (8,9). Skull metastasis occurs presumably via Batson's venous plexus (10,11).

Because the visual field defect improved markedly after surgical intervention, we postulate that it was caused entirely by mass effect from the skull metastasis. Whether removal of this solitary metastasis also prolongs survival is uncertain.

Acknowledgment

The authors thank Professor Jung-Chung Lin and Barry Lee Reynolds for assistance with the manuscript.

REFERENCES


Presumed Bilateral Optic Nerve Sheath Meningiomas Presenting as Optic Neuritis

Raja A. Sawaya, MD, Charif Sidani, MD, Nadim Farah, MD, and Roula Hourani-Risk, MD

Abstract: A 30-year-old man who developed acute blurred vision in the right eye and right periocular pain on eye movement proved to have a bilateral optic neuropathy and imaging evidence suggestive of bilateral optic nerve sheath meningiomas. This is an unusual presentation for optic nerve meningioma but a reminder that this entity may mimic optic neuritis.

Departments of Neurology (RAS), Diagnostic Radiology (CS, RH-R), and Ophthalmology (NF), American University of Beirut Medical Center, Beirut, Lebanon.

Address correspondence to Raja A. Sawaya, MD, Associate Professor of Clinical Medicine, Neurologist, Director Clinical Neurophysiology Laboratory, American University Medical Center, PO Box 113-6044/C-27, Beirut, Lebanon; E-mail: rs01@aub.edu.lb

A 30-year-old healthy man presented with a 1-week history of blurred vision in the right eye and mild right eye pain upon eye movement. He had no headache, diplopia, or other neurologic symptoms.

Examination revealed a best-corrected visual acuity of 20/25 in the right eye and 20/20 in the left eye. An afferent pupillary defect was present in the right eye. The external ocular examination was otherwise normal. Mild optic disc edema of the right eye was visible on ophthalmoscopy. Results of the rest of the cranial nerve and neurologic examination were normal.

Visual fields, performed on the Octopus perimeter, were normal in the left eye but showed a dense nerve fiber bundle defect concentrated mainly in the inferior field of the right eye (Fig. 2).

Visual evoked potentials were severely delayed in both eyes with P100 latencies of 139 ms in the right eye and 133 ms in the left eye (Fig. 3). Optic neuritis of the right eye and a subclinical optic neuropathy of the left eye were diagnosed.
FIG. 2. Octopus perimetry shows a mostly inferior nerve fiber bundle defect in the right eye and no definite abnormalities in the left eye.

To our surprise, MRI revealed thickening and abnormal enhancement of the posterior intraorbital optic nerve sheaths bilaterally, extending into the optic canals, tuberculum sella, right anterior clinoid process, and planum sphenoidale (Fig. 1). Nonenhanced CT of the orbits revealed plaque-like calcifications along the optic nerve sheaths (Fig. 4). These imaging findings were consistent with a tuberculum sellae meningioma extending along the planum sphenoidale and into both orbits. The patient did not receive any treatment and is being followed closely for deterioration of vision.

Meningiomas that affect the optic nerve sheath meningiomas are bilateral in about 5% of patients (1). In fact, bilateral involvement is so rare in meningiomas originating within the intraorbital sheath that it suggests an origin from the planum sphenoidale or tuberculum sella with secondary extension to the intraorbital optic nerve sheaths (2,3). What makes our patient unusual is that the presentation of unilateral visual loss was acute and associated with ipsilateral periocular pain. Such a presentation justifiably raised the suspicion of optic neuritis. MRI of the optic nerves revealed the bilateral abnormalities, which can sometimes be mimicked by inflammation. CT is helpful in distinguishing a meningioma from inflammation by showing calcification (4,5).
Optic Nerve Sheath Meningiomas

FIG. 3. Visual evoked potentials show prolonged P100 latencies in both eyes.

FIG. 4. Precontrast axial CT reveals thickening and calcification in the region of the orbital optic nerves bilaterally.

REFERENCES

Neuro-Ophthalmologic Manifestations of Paraneoplastic Syndromes

Melissa W. Ko, MD, Josep Dalmau, MD, PhD, and Steven L. Galetta, MD

Abstract: Paraneoplastic syndromes with neuro-ophthalmologic manifestations may involve the central nervous system, cranial nerves, neuromuscular junction, optic nerve, uvea, or retina. Most of these disorders are related to immunologic mechanisms presumably triggered by the neoplastic expression of neuronal proteins. Accurate recognition is essential to appropriate management.

PARANEOPLASTIC CEREBELLAR DEGENERATION

Paraneoplastic cerebellar degeneration (PCD) is a syndrome of subacute severe pancerebellar dysfunction (Table 1). Initially, patients present with gait dysfunction. Over several days to weeks, they develop truncal ataxia, limb ataxia, dysarthria, and dysphagia. The cerebellar disease eventually stabilizes but leaves patients incapacitated.

PCD is most commonly associated with cancers of the lung, ovary, and breast and with Hodgkin disease (7). Ocular motor manifestations include nystagmus, ocular dysmetria, saccadic pursuit, saccadic intrusions and oscillations, and skew deviation (8). Over the last 30 years, at least nine anti-neuronal antibodies have been associated with PCD. However, only about 50% of patients with suspected PCD test positive for anti-neuronal antibodies in serum or cerebrospinal fluid (CSF) (9). Anti-Yo and anti-Tr are the autoantibodies most commonly associated with a pure paraneoplastic cerebellar syndrome (Table 2). PCD is pathologically characterized by severe, diffuse cerebellar Purkinje cell loss with proliferation of Bergmann glia and sometimes infiltrates of inflammatory cells in the deep cerebellar nuclei.

PCD associated with anti-Yo is usually found in postmenopausal women with breast or ovarian cancer presenting at approximately 60 years of age. Peterson et al (10) reported that of 55 patients positive for anti-Yo antibody, all had findings of horizontal nystagmus (Table 3). Some had downbeat nystagmus with an additional rotatory or vertical component. Diplopia was present in approximately one third of these patients. Rare neuro-ophthalmologic findings included opsinclonus and progressive visual loss. Cohen et al (11) reported a patient with anti-Yo PCD who had recurrent anterior uveitis, upward gaze palsy with eyelid retraction, bilateral sixth cranial nerve palsies, and skew deviation. The initial search for a malignancy was negative. However, an update to the case reported 5 years later indicated that a poorly differentiated carcinoma, probably of breast origin, in a right axillary lymph node was found on positron emission tomography (PET) and confirmed by biopsy. This carcinoma had strong expression of Yo antigen (12). Prognosis in anti-Yo PCD is generally...
Table 1. Paraneoplastic syndromes of neuro-ophthalmologic significance

<table>
<thead>
<tr>
<th>Paraneoplastic encephalitides</th>
<th>Brain stem</th>
<th>Encephalomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ma2 encephalitis</td>
<td>Anti-NMDA receptor encephalitis</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic cerebellar degeneration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opsoclonus-myoclonus</td>
<td>Lambert-Eaton myasthenic syndrome</td>
<td></td>
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<tr>
<td>Paraneoplastic stiff-person syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic syndromes of retina and optic nerves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic retinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer-associated retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma-associated retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral diffuse uveal melanocytic proliferation</td>
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<td></td>
</tr>
</tbody>
</table>

NMDA, N-methyl-D-aspartate.

poor, with many patients becoming non-ambulatory within 3 months (13,14). Most patients have been reported to die of neurologic causes (10,15), but Rojas et al (13) found this to be the case in only 29%.

PCD associated with Hodgkin disease is more commonly found in men with a median age of 54 years, reflecting the bimodal age distribution of Hodgkin disease—one peak occurring in young adulthood and a second peak occurring after age 50 (16). In addition to the cerebellar symptoms of anti-Tr PCD and Hodgkin disease, neuro-ophthalmologic manifestations include downbeat nystagmus, diplopia, oscillopsia, and vertigo. Bernal et al (17) reported that 2 of 28 patients with anti-Tr PCD developed reversible encephalopathy and optic neuritis. The overall prognosis of anti-Tr PCD is better than that of anti-Yo PCD. In one review of 50 cases of PCD (14), patients with anti-Tr PCD had a median survival from time of diagnosis of longer than 117 months compared with patients with anti-Yo PCD, for whom median survival from time of diagnosis was only 13 months.

PCD associated with small-cell lung cancer (SCLC) usually relates to several paraneoplastic antibodies, including anti-Hu, voltage-gated calcium channel (VGCC) antibodies, and infrequently anti-CV2/collapsin response-mediating protein-5 (CRMP-5). Patients with anti-Hu antibodies may present with subacute cerebellar dysfunction in the seventh decade that initially resembles pure PCD in up to 20% of patients. Eventually these patients develop additional neurologic or neuro-ophthalmologic symptoms of brain stem or limbic encephalitis and peripheral neuropathy (14,18,19). Autonomic dysfunction with the development of unilateral or bilateral tonic pupils has been reported in patients with SCLC and anti-Hu antibodies (20–22). Neurologic outcome is generally poor; 75% of patients become bedridden with a median survival of 7–11 months (14,18). Patients with PCD and SCLC who do not have anti-Hu antibodies often harbor VGCC antibodies. These patients may have overlapping manifestations of Lambert-Eaton myasthenic syndrome (see below) (19,23).

For all immunologic types of PCD, CSF studies may show a mild lymphocytic pleocytosis with elevated protein, oligoclonal bands, elevated immunoglobulin synthesis, and negative cytology in approximately 60% of patients. Brain MRI is usually normal at presentation but shows cerebellar atrophy with enlargement of the fourth ventricle and cerebral and cerebellar sulcal prominence in advanced cases (19).

Treatment is directed to the underlying malignancy, although PCD in most patients does not improve with cancer treatment. There are only a few reported cases of improvement or stabilization of PCD after treatment of the neoplasm (15,24–26). Plasmapheresis or immunosuppression (cyclophosphamide or corticosteroids), sometimes used in conjunction with intravenous immunoglobulin (IVIg) and tumor treatment, have shown improvement in several reports (27,28). A study suggested that the likelihood of neurologic improvement after IVIg treatment is higher in those treated within the first month of developing cerebellar dysfunction (29,30).

Paraneoplastic Brain Stem Encephalitis

Brain stem encephalitis due to paraneoplastic disease can present with various neurologic and neuro-ophthalmologic symptoms and signs, depending on whether the rostral or caudal portions of the brain stem are involved. When midbrain brain stem structures are involved, patients may have palsy, vertical gaze paresis, and nystagmus (31). Pontine and medullary damage can result in vertigo, hearing loss, facial numbness, dysphagia, dysarthria, and hoarseness. Patients may complain of diplopia and oscillopsia with signs of vertical nystagmus, upbeat or downbeat nystagmus, horizontal gaze paresis, internuclear ophthalmoplegia, skew deviation, sixth cranial nerve paresis, impairment of facial sensation, hyperactive gag reflex or jaw jerk, and weakness of the tongue or palatal muscles (8). The antibodies frequently associated with paraneoplastic brain stem encephalitis include Hu, CV2/CRMP-5, Ma-2, and NMDA receptor.

Paraneoplastic Encephalomyelitis

Paraneoplastic encephalomyelitis (PEM) refers to an immune-mediated inflammatory disorder that affects the
TABLE 2. Anti-neuronal antibodies with associated tumors and paraneoplastic syndromes

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Associated cancer</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu (ANNA-1)</td>
<td>Small cell lung cancer, other</td>
<td>Eencephalomyelitis, brain stem encephalitis, paraneoplastic cerebellar degeneration, sensory neuropathy, autonomic dysfunction</td>
</tr>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>Ovary, lung</td>
<td>Brain stem encephalitis, paraneoplastic cerebellar degeneration, opsoclonus</td>
</tr>
<tr>
<td>Anti-Ri (ANNA-2)</td>
<td>Breast, small cell lung cancer</td>
<td>Brain stem encephalitis, paraneoplastic cerebellar degeneration, opsoclonus</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Hodgkin lymphoma</td>
<td>Brain stem encephalitis, paraneoplastic cerebellar degeneration, opsoclonus</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Testicular germ cell tumor, others</td>
<td>Limbic and brain stem encephalitis, Stiff-person syndrome, encephalomyelitis</td>
</tr>
<tr>
<td>Anti-ampiphysin</td>
<td>Breast, small cell lung cancer</td>
<td>Encephalomyelitis, paraneoplastic cerebellar degeneration, opsoclonus</td>
</tr>
<tr>
<td>Anti-CRMP-5 (anti-CV2)</td>
<td>Small cell lung cancer, other</td>
<td>Encephalomyelitis, paraneoplastic cerebellar degeneration, opsoclonus</td>
</tr>
<tr>
<td>Anti-NMDA receptor</td>
<td>Teratoma</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Anti-P/Q type voltage-gated calcium channel</td>
<td>Small cell lung cancer</td>
<td>Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration</td>
</tr>
<tr>
<td>Anti-acetylcholine receptor</td>
<td>Thymoma</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Anti-recoverin</td>
<td>Small cell lung cancer</td>
<td>Cancer-associated retinopathy</td>
</tr>
<tr>
<td>Anti-bipolar cells</td>
<td>Melanoma</td>
<td>Melanoma-associated retinopathy</td>
</tr>
</tbody>
</table>

ANNA, anti-neuronal nuclear protein-5; PCA-1, perkinje cell antibody-1; NMDA, N-methyl-d-aspartate; CRMP-5, collapsin response-mediating protein-5.

central nervous system, dorsal root ganglia, and autonomic nerves. Neuro-ophthalmologic findings are common in patients with predominantly brain stem and cerebellar dysfunction. The antibody most frequently encountered is anti-Hu, and the underlying tumor is usually SCLC.

**ANTI-MA2 ENCEPHALITIS**

Anti-Ma2 encephalitis is characteristically associated with limbic, diencephalic, and brain stem dysfunction. In young men, the tumor most frequently involved is a germ-cell neoplasm of the testis; in older men and women, lung and breast cancers are the predominant tumors (32,33).

In a study of 38 patients with anti-Ma2 encephalitis (32), 25 had brain stem signs; 92% of these patients had eye movement abnormalities, and 60% had vertical gaze paresis that eventually developed into severe or total paralysis. Most patients initially developed difficulty with upward saccades, but a few patients presented with downward gaze paresis. Vestibulo-ocular reflexes and the Bell phenomenon were usually preserved until later in the disease. Posis was present in almost 20% of the patients, but the exact mechanism was not elucidated. We have seen patients with paraneoplastic syndromes presenting with apraxia of eyelid opening and ptosis; the latter may relate to loss of neurons in the central caudal subnucleus of the oculomotor nucleus (31). Other neuro-ophthalmologic findings were oculogyric crisis, opsoclonus, ocular flutter, and nystagmus. Bennett et al (34) reported two patients with anti-Ma2 encephalitis who had supranuclear gaze palsy, skew deviation, and an ocular tilt reaction. One patient had bilateral visual loss related to a chronic inflammatory infiltrate that involved the diencephalon, established by brain biopsy; the other patient had upbeat nystagmus in downgaze and a monococular pendular nystagmus. Less common neurologic manifestations in anti-Ma2 encephalitis include parkinsonism and a severe hypokinetic syndrome.

Brain MRI typically shows T2/FLAIR hyperintensities in the brain stem and limbic structures that may enhance on postcontrast T1 sequences (32). In a review of 38 cases (35), 16% of patients with anti-Ma2 encephalitis had been initially considered to have Whipple disease and had undergone duodenal biopsy.

In most patients with testicular cancer, the tumor is identified clinically or by ultrasound, but Mathew et al (36) described six men younger than age 50 who had no evidence of tumor in the setting of anti-Ma2 progressive neurologic deficits. After orchiectomy, all six were found to have a microscopic intratubular germ-cell neoplasm of unclassified type (IGCNU), a common precursor of testicular cancers.

Aggressive search for and treatment of the underlying malignancy in this disorder is important because about one third of patients show improvement after tumor removal.
and immunotherapy, which may include corticosteroids, IVlg, or plasma exchange (32,37).

**ANTI-NMDA RECEPTOR ENCEPHALITIS**

Patients with this disorder develop a highly characteristic syndrome that evolves in stages, consisting of a prodromal low-grade fever and headache followed by prominent psychiatric symptoms or short-term memory loss, along with visual hallucinations, seizures, progressive unresponsiveness, hypoventilation, autonomic instability, and dyskinesias. The disorder usually affects young women with mature or immature ovarian teratomas. All patients harbor serum and CSF antibodies to NR1/NR2 heteromers of the NMDA receptor (38). Some patients present with oculogyric crises in association with orofacial and limb dyskinesias. Opsoclonus has also been observed in some patients with mature teratomas without antibodies to the NMDA receptor. In addition, a patient developed transient inverse ocular bobbing (also known as ocular dipping) while she was in the intensive care unit recovering from anti-NMDA receptor encephalitis (H. Shimazaki, MD, written communication, November 2007). Despite the severity of the disorder, patients usually recover after tumor removal and immunomodulation.

**OPSOCLONUS-MYOCLOONUS SYNDROME**

Opsoclonus, which may be of metabolic, infectious, or paraneoplastic origin, consists of involuntary, arrhythmic, multidirectional saccades that are irregular in amplitude and frequency without an intersaccadic interval (39). In a paraneoplastic setting, it generally includes encephalitis, myoclonus, and ataxia of the trunk and limbs [opsoclonus-myoclonus syndrome (OMS)].

The most common underlying malignancy in children with this syndrome is neuroblastoma. Children (more often girls) generally are seen between the ages of 8 months and 3 years with a peak incidence at 18 months (40,41). More than 50% of children with opsonoclonus have neuroblastoma, whereas only 2% of children with neuroblastoma present with OMS (41). In adults, there is no gender predilection. Occult malignancies are found in approximately 20% of adults presenting with opsonoclonus (42), most often involving the lung (especially SCLC), ovaries, uterus, or breast. OMS associated with thymoma and melanoma has been reported (43,44).

Patients with paraneoplastic OMS are often seronegative for anti-neuronal antibodies; exceptions include those with OMS associated with anti-Ri (45-47) and anti-amphiphysin antibodies (48). Reports of patients with opsonoclonus and cerebellar or brain stem encephalitis associated with anti-Hu (49–51), anti-Yo (10), and anti-Ma2 (32) are rare. The pathophysiology of OMS is unknown, but it is suspected to be of autoimmune origin, supported by the detection of CSF inflammatory findings, a clinical response to immunotherapy, and the presence of anti-neuronal antibodies in serum and CSF (48).

Management of OMS involves an aggressive search for an underlying neoplasm and its treatment. Because neuroblastoma is so commonly associated with opsonoclonus in children, it is imperative to exclude it. A complete screening protocol for neuroblastoma in a child with opsonoclonus or ocular flutter would include 1) urine vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels, 2) MRI of neck, chest, abdomen, and pelvis, and 3) metaiodobenzylguanidine (MIBG) whole-body scintigraphy if results of MRI are unrevealing.

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**TABLE 3. Paraneoplastic syndromes/antibodies organized by neuro-ophthalmologic signs and symptoms**

<table>
<thead>
<tr>
<th>Neuro-ophthalmologic findings</th>
<th>Anti-Yo</th>
<th>Anti-Hu</th>
<th>Anti-Ma2</th>
<th>Anti-Ri</th>
<th>Anti-VGCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal saccades</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ MG</td>
</tr>
<tr>
<td>External ophthalmoplegia</td>
<td>+ *</td>
<td>+ *</td>
<td>+ *</td>
<td>+ *</td>
<td>+ *</td>
</tr>
<tr>
<td>Eyelid retraction</td>
<td>+ ↔ ↓</td>
<td>+ ↑</td>
<td>+ ↑</td>
<td>+ ↑</td>
<td>+ ↑</td>
</tr>
<tr>
<td>Internuclear ophthalmoplegia</td>
<td>+ ↔ ↓</td>
<td>+ ↑</td>
<td>+ ↑</td>
<td>+ ↑</td>
<td>+ ↑</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ocular dysmetria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Oculogyric crisis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Opsoclonus</td>
<td>+ *</td>
<td>- *</td>
<td>- *</td>
<td>- *</td>
<td>+</td>
</tr>
<tr>
<td>Optic disc edema</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Photopsias</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Progressive visual loss</td>
<td>+ *</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

↓, downbeat; ↔, horizontal; VGCC, voltage-gated calcium channel; CRMP-5, collapsin response-mediating protein-5; NMDA, N-methyl-d-aspartate.

*Rare presentation.*
The combination of MRI and MIBG may be necessary because false-negative and -positive results can occur with each test in this setting (52). Standard treatment of children with OMS includes corticosteroids, such as prednisone and adrenocorticotropic hormone (ACTH), which provide some symptomatic improvement but are often associated with long-term adverse side effects (53,54). Rostasy et al (55) reported the use of high-dose pulse dexamethasone in 11 children with OMS, showing complete and sustained remission in approximately 50% with few side effects. Other treatments reported in children include IVIg, cyclophosphamide, and rituximab (56,57) with variable success. Removal of the neuroblastoma alone has not improved symptoms in most patients (53,58). In adults, there have been a few reports of neoplasm resection leading to complete resolution of OMS (59–61). Corticosteroids are not as effective in reversing adult OMS as in reversing childhood OMS (62). Treatments with reported clinical improvement include clonazepam (63), IVIg (50), and immunoadsorption (64,65).

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the neuromuscular junction caused by antibodies against the VGCC, resulting in a decrease in acetylcholine release at the presynaptic level. LEMS can present in paraneoplastic or primary autoimmune forms, which have identical clinical and pathophysiologic features. Approximately 50% of patients with LEMS have SCLC, whereas the incidence of LEMS in patients with SCLC is only 3% (66). Patients usually present with proximal muscle weakness, autonomic dysfunction, and decreased deep tendon reflexes.

Unlike myasthenia gravis (MG), in which ptosis and diplopia are common manifestations, such signs and symptoms can occur but are generally considered uncommon in LEMS (67,68). Nonetheless, in a series of 50 patients with LEMS, O’Neill et al (67) reported diplopia in 25 (50%) and ptosis in 27 (54%). In another series of 23 patients with LEMS without coexistent MG (69), more than 78% had diplopia, ptosis, dysarthria, or dysphagia. In 30% of these patients, these features were the chief complaint. This study emphasized the fact that some cases of LEMS may be under-recognized because the neuro-ophthalmic findings are often attributed to MG (69,70). Rudnicki (71) reported a patient with LEMS, SCLC, and VGCC antibodies who had diplopia and ptosis as the only clinical manifestations. These manifestations resolved after chemotherapy without further development of neurologic findings.

Ductional deficits are common in patients with MG but are rare in patients with LEMS, with only three cases reported. Only one of these cases was a patient who had LEMS as the only diagnosis; the other two involved patients with overlapping MG (72–74). Other associated features of LEMS include involuntary eyelid closure (74) and dilated, poorly reactive pupils (75,76). Sluggish pupillary reactivity may be a result of autonomic dysfunction in LEMS (77), a feature that would clinically distinguish it from MG. Another clinical feature that may distinguish LEMS from MG is improvement of ptosis with sustained upgaze in patients with LEMS (78), a phenomenon perhaps due to facilitation of the levator muscle after exercise.

The mainstay of diagnostic evaluation in LEMS is electromyography (EMG), with its characteristic findings of
low amplitude resting compound muscle action potentials (CMAPs), a decremental CMAP with low stimulation rates (2–5 Hz), and an incremental CMAP with high stimulation rates (30–50 Hz). An immunosassay for VGCC antibodies is confirmatory in patients with clinical and electrophysiologic features of LEMS but is not diagnostic by itself.

Central to the management of LEMS is an aggressive search for an underlying malignancy. SCLC may not be readily detected on a chest CT scan because the lesions are often very small. Thus, a more intensive search, including bronchoscopy or PET, may be warranted, especially in high-risk patients (79).

Treatment of the malignancy may improve symptoms of LEMS. If patients are still symptomatic after this treatment, medications that improve neuromuscular transmission, such as acetylcholinesterase inhibitors (pyridostigmine) or aminopyridines (3,4-diaminopyridine), may be effective. IVIg has been shown to improve weakness, but the response is temporary, requiring repeat infusions at regular intervals (80–84). Immunosuppressive agents such as prednisone or azathioprine may begin to show benefits several months after treatment is begun (85–87).

STIFF-PERSON SYNDROME

Stiff-person syndrome (SPS) is a disease characterized by insidious onset of rigidity of the truncal and proximal limb muscles with intermittent superimposed painful spasms. Symptoms are absent during sleep or anesthesia (88–90). Approximately 80% of patients with SPS have a non-paraneoplastic form of this disorder associated with polyendocrinopathies and antibodies to glutamic acid decarboxylase (GAD). The less common paraneoplastic form of SPS is associated with antibodies to amphiphysin. Malignancies most commonly involved in the paraneoplastic form of SPS are SCLC, breast cancer, and Hodgkin disease (91–93).

Neuro-ophthalmologic findings include gaze-evoked nystagmus, poor saccadic initiation, and impaired smooth pursuit (94). In patients with cerebellar dysfunction, there may be downbeat nystagmus, square-wave jerks, skew deviation, slow and hypometric saccades, and impaired smooth pursuit in downward gaze (95–97). The suspected pathophysiology is dysfunction of GABAergic pathways from anti-GAD antibody activity, particularly involving connections within the cerebellum and with the brain stem (94).

There is a report of SPS occurring in conjunction with MG in a patient with bilateral abduction deficits, nystagmus, impairment of horizontal and vertical saccades, but no ptosis. This patient had almost complete resolution of SPS and myasthenic findings after removal of a thymoma (98).

Treatment centers on baclofen or diazepam, which enhance central gamma-aminobutyric acid (GABA) activity, and immunomodulation. Patients with SPS receiving high-dose IVIg treatment have had reduced stiffness and falls and improved ambulation and performance in work-related or household tasks. The duration of benefits can range from 6 weeks to 1 year (99-101).

CANCER-ASSOCIATED RETINOPATHY

Cancer-associated retinopathy (CAR) was first recognized in three patients who had a visual disturbance before the diagnosis of their cancers (102). Autopsy findings showed photoreceptor degeneration without co-existent neoplastic involvement of the orbit, eye, or optic nerve. In the early 1980s, Keltner et al (103) reported a patient with paraneoplastic retinopathy and demonstrated retinal antibodies reacting against photoreceptor cells. In a series of three patients with CAR, Thrillik et al (104) found an antibody that bound to a 23-kDa retinal antigen. It was later named “recoverin” and identified as a Ca

2+

-binding photoreceptor protein that controls phosphorylation of the visual receptor rhodopsin by inhibition of rhodopsin kinase (105). Although recoverin is the most common antigen linked with CAR, more than 20 other antigens have since been identified, including a 65-kDa heat shock cognate protein (106), a 48-kDa protein (107), an enolase (108), a photoreceptor nuclear receptor (109), and neurofilaments (110). These findings suggest that CAR represents the clinical manifestations of a multiplicity of autoimmune reactions (8,111).

Patients with CAR generally present with symptoms of painless progressive visual dimming and photopsias. They have a constellation of visual symptoms attributable to rod dysfunction (impaired dark adaptation and peripheral visual field loss) and cone dysfunction (decreased visual acuity, central scotomas, color dysfunction, photosensitivity, and glare after light exposure).

On examination, patients have bilateral ocular involvement with a decrease in visual acuity, color discrimination, and visual field that includes central or ring scotomas with preserved islands of vision. Results of ophthalmoscopy at symptom onset may be unremarkable but shortly thereafter may show arteriolar narrowing, retinal pigment epithelial alteration with thinning and mottling, and optic disc pallor. Vitreous and anterior chamber cells may be seen. Electroretinography (ERG) shows undetectable or substantially decreased responses due to photoreceptor degeneration. Results of CSF studies can range from normal to showing mild lymphocytic pleocytosis and elevated protein.

CAR is most commonly associated with SCLC and less commonly with non-small cell lung, ovarian, cervical, and endometrial cancers. Rare reports of colon carcinoma (112) and invasive thymoma (113,114) have also appeared.
For many years, corticosteroids were the mainstay of treatment but produced disappointing results. Guy and Aptsiauri (115) reported two patients with a mild to moderate response to IVIg. Espandar et al (116) have reported a patient with CAR who had a favorable response to alemtuzumab, a monoclonal antibody against the cell surface glycoprotein CD52 expressed on B and T lymphocytes, monocytes, and macrophages. The patient's symptoms had not improved after plasma exchange and cyclosporine treatment, but for 8 years the patient had several episodes of relapsing-remitting retinopathy, which improved each time after alemtuzumab treatment. Much more study will be needed to determine whether any of these treatments is truly effective.

MELANOMA-ASSOCIATED RETINOPATHY

Melanoma-associated retinopathy (MAR) is a rare visual paraneoplastic syndrome with fewer than 100 reported cases (117–119). Patients with MAR frequently have an established diagnosis of cutaneous melanoma with visual problems developing months to years later. There is never any evidence of ocular or other metastasis at the time that visual symptoms begin. The proposed pathophysiology involves a B-lymphocyte response to the production of autoantibodies against an unknown melanoma antigen that cross-reacts with retinal components, particularly bipolar cells (120–122).

In a review of 62 cases, Keltner et al (117) found that the average patient age at presentation was 57.5 years, ranging from 30 to 78 years. Men were more frequently affected than woman, and visual acuity at presentation was 20/60 or better in 82% of patients. Common symptoms included shimmering, flickering or pulsating photopsias, progressive vision loss over months, and night blindness. MAR differs from CAR in that visual acuity and color vision are usually normal or near normal (Table 4). Initial fundus findings may be normal, but retinal vessel narrowing, retinal pigment epithelium changes, and optic disc pallor have been noted several months after presentation. Although manifestations may initially be limited to one eye, the disorder eventually affects both eyes within weeks to months. Visual fields may be completely normal or show peripheral constriction, generalized depression, or paracentral or mid-peripheral scotomas. Central scotomas are less common in MAR than in CAR. The ERG shows reduced or absent b-waves with normal dark-adapted a-waves indicating bipolar cell dysfunction (123,124). CSF constituents are normal.

There is no certifiably effective treatment for MAR. Radiation therapy, IVIg, cytoreductive (debulking) surgery, and intravenous (IV) corticosteroids with plasmapheresis have been associated with improved visual acuity and visual field (117). In the large review by Keltner et al (117), four of seven patients with MAR who experienced visual improvement had undergone cytoreductive surgery, received IVIg, or both. Corticosteroids alone have not been associated with symptomatic improvement. Reducing the tumor burden may be important, as emphasized by the case of a patient who had worsening visual acuity every time metastases recurred and improvement when radiation therapy reduced the size of the metastases (117).

<table>
<thead>
<tr>
<th>TABLE 4. Comparison of cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presenting age (range)</strong></td>
</tr>
<tr>
<td><strong>Gender predilection</strong></td>
</tr>
<tr>
<td><strong>Presenting visual acuity</strong></td>
</tr>
<tr>
<td><strong>Timing of ophthalmic manifestations in relation to diagnosis of malignancy</strong></td>
</tr>
<tr>
<td><strong>Ophthalmoscopy</strong></td>
</tr>
<tr>
<td><strong>Electroretinography</strong></td>
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<tr>
<td><strong>Survival time after cancer diagnosis</strong></td>
</tr>
<tr>
<td><strong>Antibody</strong></td>
</tr>
</tbody>
</table>

PARANEOPLASTIC OPTIC NEUROPATHY

Paraneoplastic optic neuropathy (123) is a rare disorder characterized by painless visual loss and optic disc edema. Associated manifestations may include ophthalmoplegia (125,126), retinitis (127), subacute cerebellar syndrome (128–132), and other neurologic deficits.
Patients with PON present between the ages of 50 and 75 years with a history of heavy smoking; men and women are equally affected. Painless visual loss occurs over weeks to months, ultimately involving both eyes. Most patients also have ataxia, movement disorders, cranial nerve abnormalities, cognitive impairment, seizures, neuropathy, autonomic instability, or myelopathy. Neuro-ophthalmologic manifestations include vertical gaze paresis, opso-clonus, and bilateral internuclear ophthalmoplegia (127, 129). Edematous optic discs, vitreous cells, and visual field defects are often present on examination. The paraneoplastic antibody most frequently identified is CV2/CRMP-5.

Mild enhancement of the optic nerve has been reported on MRI (133). Fluorescein angiography may show optic disc hyperfluorescence and leakage. Full-field ERG has shown prolongation of the scotopic combined rod-cone response, the photopic cone response, and the photopic 30-Hz flicker response (127). Based on the small number of patients, the neurologic and visual prognosis for PON seems to be dependent on how well patients have responded to treatment of their underlying malignancy (131, 132).

**BILATERAL DIFFUSE UVEAL MELANOCYTIC PROLIFERATION**

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is an uncommon paraneoplastic entity in which an underlying tumor causes diffuse bilateral proliferation of melanocytes in the uveal tract, leading to bilateral visual loss. Approximately 30 cases have been reported (134, 135).

BDUMP was first described in 1966 by Machemer (136) in a 57-year-old man with bilateral visual loss, cataracts, and retinal detachments. The histopathology of the eyes showed diffuse choroidal and ciliary body thickening. The patient had a retroperitoneal mass suspected to be a pancreatic cancer, but a postmortem study was never performed because the patient died several days after exploratory laparotomy.

In women, carcinoma of the reproductive tract is often found; in men, carcinomas of the lung and pancreas are most common. Visual acuity ranges from normal to light perception. Gass et al (137) described multiple red retinal pigment epithelium (RPE) patches in the posterior pole with early fluorescein angiographic hyperfluorescence, together with multiple slightly elevated uveal melanocytic tumors and diffuse uveal tract thickening, exudative retinal detachment, and rapidly progressive cataract.

Patients of either sex generally present after age 50 with abrupt bilateral visual loss and few or no fundus findings but may range in age from 34 to 89 years. Nearly all patients have had rapid cataract progression, and all have had retinal detachment (135). The visual symptoms precede the diagnosis of a systemic malignancy. Although choroidal thickening may be diffuse on pathologic examination, it appears focal on ophthalmoscopic examination.

Some observers believe that the uveal manifestations of BDUMP represent a benign entity without a tendency to metastasize (138). This assumption has been based on the fact that most reported patients have benign-appearing melanocytes and no evidence of uveal tract metastasis. Lack of uveal melanocytic spread could be related to short survival, which might preclude identification of metastasis. In one review, the average time from presentation to death was a mean of 15 months. Some observers believe, however, that the uveal manifestations of BDUMP have metastatic potential (139). Duong et al (140) reported a patient with BDUMP associated with ovarian carcinoma who survived the ovarian cancer, but subsequently developed metastatic amelanotic malignant melanoma.

In the earliest reported cases of BDUMP, patients’ choroidal lesions were irradiated in the belief that they were malignancies, a treatment that was sometimes associated with worsening of vision. Corticosteroid treatment has also been used without visual improvement. One case report ascribed improvement in vision to treatment with external beam irradiation and subretinal fluid drainage (141).

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Expanding Access to Published Research: Open Access and Self-Archiving

Allyson Mower, MA, and Mary E. Youngkin, MLS

Abstract: Academic libraries traditionally provide access to the life science journal literature for their respective institutions by purchasing annual subscriptions to journals. However, with skyrocketing subscription prices and decreased or flattened library budgets, fewer journals are being purchased. This trend results in diminished access to the literature for members of that institution. Open access and self-archiving are possible solutions to this crisis.

One of the larger problems looming in scholarly publishing today is lack of access to published articles. Readers are irritated at being asked to make a purchase every time they need to read the work of their colleagues. This restricted, costly access to the published literature has a negative impact on scholarly communication and the advancement of science.

Much of the scientific literature remains locked behind subscription prices that not even the wealthiest academic institutions can afford. With staggering prices (Fig. 1) and 6%-12% annual increases, libraries with fixed budgets can no longer afford to purchase the bulk of science journals (1). The current system is unsustainable.

Taxpayer dollars support university facilities, salaries, and federally funded research grants. In the current publishing model, scholars generate ideas, write grants, do the research, put together articles detailing the results of their work, and conduct peer review without remuneration. To have their work seen and cited in prestigious journals, authors sign over copyright control of their work to publishers. This control has given publishers the ability to set unaffordable prices. University libraries then buy back from publishers the very content their scholars have created. Access for universities, scholars, and consumers is entirely dependent upon ability to pay.

Ultimately this situation interferes with the production of new scientific information. If the library at an academic institution can only afford to purchase a portion of the body of life science journals, a scholar’s level of access to research at that institution is severely constrained. Authors move from article to article until one can be found at no cost or send a request to the primary author for a copy. Both of these methods are poor solutions and lead to a decline in readership and citations. Researchers have found that “90% of papers that have been published in academic journals are never cited. Indeed, as many as 50% of papers are never read by anyone other than their authors, referees and journal editors” (2).

Open Access Publishing

Publishing in open access (OA) journals and self-archiving are more viable solutions. Some studies have estimated that OA articles are cited 50%-250% more often than non-OA articles (3). The Internet has enabled OA literature to be “digital, online, free of charge, and free of most copyright and licensing restrictions” (4).

Under an OA business model, such as those used by BioMed Central and Public Library of Science, the author, rather than the subscriber, pays the article processing charges which usually range from $500 to $2,500, depending on the journal. This approach provides, among other services, immediate access to the article for any Internet user. The fees cover the costs of “developing and maintaining electronic tools for peer-review, preparing the article in various formats for online publication, securing inclusion in PubMed as soon as possible, securing inclusion of full-text in a number of permanent archives such as PubMed Central and securing inclusion in CrossRef, which enables electronic citation in other journals that are available electronically” (5). This type of publishing and scholarly communication model makes obtaining an article immediate, direct, efficient, and equitable.

Digital Repositories and Libraries

Digital repositories and libraries also provide content freely to the world and offer authors the means to

University of Utah Eccles Health Sciences Library, Salt Lake City, Utah.
Address correspondence to Allyson Mower, University of Utah Eccles Health Sciences Library, 10 North 1900 East, Bldg. 589, Salt Lake City, UT 84112; E-mail: amower@lib.med.utah.edu

self-archive. The National Library of Medicine created PubMed Central (6) as a digital repository to facilitate free access to National Institutes of Health (NIH)–funded life science research. Other digital repositories include the National Science Digital Library (NSDL) (7), Health Education Assets Library (HEAL) (8), eSciDoc (9), and other subject and institutional repositories such as arXiv.org (10), Neuro-Ophthalmology Virtual Education Library (NOVEL) (11), and DSpace at MIT (12). These systems aim to provide current quality, peer-reviewed, and open scientific content via the Web. Furthermore, these systems intend to go beyond the provision of traditionally published, text-based research articles to provide access to intellectual content such as oral presentations, images, Web pages, audio, video, and interactive media. These resources can be hyperlinked, making it quite easy for a researcher to discover and navigate to additional and relevant research.

**SELF-ARCHIVING**

A broad range of research materials are becoming freely available from a desktop by simply using a search
engine such as Google Scholar. There are many ways for authors and users to propel this new development. The simplest method, called self-archiving, allows researchers to deposit a copy of their final peer-reviewed manuscript into their institution's digital repository (Fig. 2), an act that "takes a few minutes and costs a scientist nothing...at a stroke, by self-archiving, a scientist can banish the threat of that bane of scientific life—obscurity" (13).

Researchers can also retain key portions of their copyright so that they may post publishers' versions of articles in repositories or on departmental Web sites. A balanced approach, as promulgated by the group Scholarly Publishing and Academic Resources Coalition (SPARC), involves having publishers retain nonexclusive rights to publish and make financial gains and for authors to retain their rights to reprint and make derivative works. Authors may promote this approach by using an addendum to the original transfer agreement. SPARC provides such a document (14).

It is, of course, naive to think that authors will stop publishing in prestigious journals that facilitate promotion and tenure simply for the sake of enhancing access for others. Many young scholars and researchers consider that they have much to lose in terms of career advancement by pushing for change at pivotal points in their careers. Some university departments recognize this concern and have begun addressing the standard retention, promotion, and tenure process by initiating a debate about what constitutes a "published" paper (15). The appropriate process of peer review is also under review. There are some who believe that because most university faculty provide peer review at no cost to the publisher, there ought to be a new system in which scholars and researchers interact more directly (yet anonymously) via digital scientific communities such as arXiv.org rather than through traditional publishing hierarchies.

In our networked and digital environment, a lot remains at stake for scholarly communication. Scientists and scholars can advance their research by publishing and/or self-archiving in dynamic, interoperable, efficient, and open systems to deliver the results of life science research to all who wish to read it.

REFERENCES
Open Access Mandate Threatens Dissemination of Scientific Information

Erin McMullan

Abstract: The public good is served when researchers can most easily access current, high-quality research through articles that have undergone rigorous peer review and quality control processes. The free market has allowed researchers excellent access to quality research articles through the investment of societies and commercial publishers in these processes for publication of scholarly journals in a wide variety of specialty and sub-specialty areas. Government legislation mandating "open access" to copyrighted articles through a government Web site could result in a reduction of financially sustainable peer-reviewed journals and a reduction in the overall quality of articles available as publishers, societies, and authors are forced to hand over their intellectual property or restrict the peer review process because of lost sales opportunities. The public is best served when the work of researchers advances science to its benefit. If researchers have fewer current resources, diminished quality control, or access to fewer trusted peer-reviewed journals, the public could ultimately lose more than it could gain from open access legislation.

Publisher investment in electronic tools has allowed dramatic increases in access and functionality for researchers. Tools now allow complex searches of current material and archives, viewing or printing of full text articles, export of content to other databases or programs, receipt of E-mail alerts when new articles on selected topics are released, and instant links to cited articles. CrossRef (http://www.crossref.org) is an example of one initiative in which publishers have worked together to broaden the impact of technical improvements for the benefit of researchers. More time can be spent analyzing, not gathering, information, with the result that 25% more articles are being accessed per year than in the print-only era (1). Investment in online submission systems has opened a floodgate of manuscript submissions globally. As submissions increase, so does the number of articles that are vetted and improved through peer review and ultimately published. It has been estimated that the number of research articles published each year grows by 3%-4% annually (2). Journal customers are typically accessing more articles, as well as non-journal online content such as videos and podcasts. The current model allows for wide distribution of research material through major academic centers, public libraries, state universities, and online databases through subscriptions, society memberships, pay-per-view, and interlibrary loan. In fact, more than 75% of researchers globally indicate that they have greater access to research articles compared with 5 years ago (3). Developing countries have also been afforded increased access. In 2002, six publishing companies partnered with the World Health Organization (WHO) to establish the Health InterNetwork Access to Research Initiative (HINARI). HINARI enables developing countries to gain free or steeply discounted access to one of the world's largest collections of biomedical and health literature. Over 100 publishers now participate in HINARI, providing more than 3,750 journal titles to 2,500 universities, hospitals, medical schools, and research institutes in 109 countries (4).

Thanks to the digitalization of publishing systems, libraries now pay less per journal and per article than in the past through new licensing alternatives, consortia buying, and volume discounting. Yet budget constraints still pose
limits to acquisitions and librarians must choose among purchasing options and from the wealth of publications available in the market. Although this is a normal free market dilemma, librarians understandably want access to as many articles as possible. In answer to this challenge, the American Library Association has supported “open access” legislation.

The Consolidated Appropriations Act, 2008 (HR 2764, §218) (5), signed into law by President Bush on December 26, 2007 (6), mandates that the National Institutes of Health (NIH) require all NIH-funded investigators to submit, upon acceptance for publication, an electronic version of their final peer-reviewed manuscripts. The manuscripts will be made accessible, free of charge, to the public no later than 12 months after the official date of publication on PubMed Central. Also stipulated is that this mandate be consistent with copyright law.

However, there is an inherent violation of copyright in mandating the deposit of the publisher’s copyrighted articles in an online government site for worldwide distribution. Unlike the NIH policy of voluntary submission, this mandate requires that the NIH force authors and publishers to forfeit their copyright without compensation for their investment.

The bill specifically requires that the manuscripts be final peer-reviewed articles that have been accepted for publication in scholarly journals. Peer-reviewed and accepted articles have benefited from significant investment by the publisher, including submission through publisher-developed online tools, manuscript evaluation, the expertise of editors and reviewers, and the processes and tools used to manage peer review, accept the article, and obtain copyright. Moreover, the congressional bill sets a dangerous precedent in the eroding of intellectual property protection in the United States. It singles out manuscripts of peer-reviewed STM journals and works counter to its own tradition of enacting laws and international agreements meant to protect against piracy. Publishers who have invested in the protection of their intellectual property (passwords and user names, contracts, monitoring of online blogs to uncover misuse, and working through the American Association of Publishers [AAP] and Software and Information Industry Association to combat piracy worldwide) will essentially lose the very core of copyright protection under the law—their exclusive right to reproduce and distribute copyrighted material. Publishers will then be left without the ability to protect their content against misappropriation when the government essentially has it “sitting on the shelf” for anyone, anywhere, to download and disseminate at will.

Protection of these articles is the protection of a successful system of scientific dissemination. Through an undistorted free market, publishers and societies have launched, sustained, and made widely available the esteemed scholarly journals the NIH would depend on to provide final peer-reviewed articles. As in any market, the profits earned serve as a motivator for the quality and innovation that the researcher-customer demands.

Government interference on the premise that legislating open access is beneficial to the advancement of scholarly research and, by extension, the public good, is misguided in the opinion of many. The Partnership for Research Integrity in Science and Medicine, “The Prism Coalition” (http://www.prismcoalition.org) was formed to educate policy makers and the public about risks of government intervention in scholarly publishing.

Open access that provides free availability of significant proportions of a journal’s content may result in its cancellation and therefore undermine and destroy the peer review system upon which researchers and society depend. With the knowledge that virtually the same content will appear online free of charge, subscribers may choose to “wait it out” rather than to pay for the most up-to-date information. The result could limit the ability of commercial publishers to publish some of the journals that evaluate and review the articles. Not-for-profit learned societies who provide journal subscriptions as a primary member benefit or depend on subscription revenue to support their journals and overall mission are threatened for the same reason. Researchers, especially in small subspecialty areas, could ultimately lose these valuable resources.

Another possible implication is that journals may no longer be willing to review and accept articles with unsustainable terms attached. Acknowledging that the peer review system is integral to quality research articles, the NIH states: “Peer review is a hallmark of quality for journals and is vital for validating the accuracy and interpretation of research results” (7). If that system is undermined through government interference, researchers would lose a valuable resource in assessing article quality.

Further, per-article and per-journal prices could increase as publishers necessarily seek to offset loss of revenue due to content released through the NIH. This may force librarians to give up journals, especially smaller niche journals, canceling paid subscriptions with current content to wait for its free release after 12 months. As a result, fewer current articles could be available upon initial publication to the researchers who need them. The negative impact of this loss would make the legislation counterproductive to the cause of advancement of scholarly research.

The public good is served when researchers can most easily access current, high-quality articles that have been through a rigorous process of peer review in a wide variety of specialty and subspecialty areas. Government legislation mandating open access through a government Web site will, it is feared, result in a reduction of sustainable
peer-reviewed journals and a reduction in overall quality as publishers, societies, and authors are forced to hand over their intellectual property or restrict the peer review process. The public is served when the work of the researchers advances science. If researchers have fewer current resources, diminished quality, or fewer peer-reviewed journals to aid in the advancement of science, the public will lose a valuable resource.

REFERENCES
Bilateral Posterior Ischemic Optic Neuropathy Associated With Use of Sildenafil

We report a case of sequential posterior ischemic optic neuropathy after the use of sildenafil. A 76-year-old man with a history of systemic hypertension, hyperlipidemia, and stroke presented to our clinic with the sudden onset of sequential visual loss in his eyes. His usual medications were 50 mg atenolol daily and 90 mg diltiazem daily for hypertension and 10 mg simvastatin daily for hyperlipidemia. In addition, he had started taking a Chinese “health product” 7 weeks earlier. His usual dose was one capsule once a day or one capsule every other day, but he had stopped it 20 days earlier until 2 days before one morning. Approximately 36 hours after ingesting the three capsules, he experienced sudden visual loss in the left eye. He awoke the next morning and discovered blurred vision in the right eye and presented to our clinic.

He reported no pain or headache or any symptoms of systemic hypotension such as dizziness, cold sweats, or feeling faint. He admitted to habitually drinking approximately 500 mL of beer a day but did not smoke. He had been compliant with his antihypertensive medications. Toxicologic analysis revealed 32.22 mg sildenafil in each capsule of the Chinese health product.

He had no light perception in either eye. Both pupils were dilated and unreactive to light. Intraocular pressures were normal, and apart from the presence of mild cataracts and cup-to-disc ratios of 0.8 bilaterally, anterior and posterior segments were normal including the retinas. Both optic discs appeared pink.

Blood pressure throughout his subsequent 5-day stay in hospital averaged 130/80 mm Hg, ranging between 120/60 and 130/90 mm Hg. Complete blood count, erythrocyte sedimentation rate, and C-reactive protein, creatinine, VDRL, folate, and vitamin B12 levels were normal. Results of liver function testing were normal apart from decreased albumin (32 g/L; normal = 37–51 g/L) and elevated -glutamyltransferase (80 IU/L; normal = 11–63 IU/L). No mitochondrial DNA mutation at nucleotides 3460, 11778, or 14484 was found. Normal = 37–51 g/L) and elevated -glutamyltransferase normal, and apart from the presence of mild cataracts and cup-to-disc ratios of 0.8 bilaterally, anterior and posterior segments were normal including the retinas. Both optic discs appeared pink.

Contrast-enhanced MRI scans with angiography of the brain and orbits was normal. Electroretinography was normal, and visual evoked potentials were absent.

After 6 weeks, visual acuity improved to count fingers in the right eye and hand movements in the left eye. Both optic discs were pale.

Nonarteritic anterior ischemic optic neuropathy has been reported to occur 30 minutes to 36 hours after ingestion of the phosphodiesterase-5 (PDE-5) inhibitor sildenafil (1,2), and a cause-and-effect relationship has been suggested. We believe our patient suffered sequential nonarteritic posterior ischemic optic neuropathy (PION), which may occur in the setting of systemic vascular disease as well as systemic hypotension. Visual loss in our patient began approximately 36 hours after a relatively large dose (96.66 mg) of sildenafil. The short duration between the onset of visual loss in both eyes in the absence of other events that would have caused a drop in blood pressure, within a relatively short interval of taking the increased dose of sildenafil, suggests a possible role for that agent in the development of his visual loss. Diltiazem may have contributed to inhibiting cytochrome P450 3A4, the isoenzyme predominantly responsible for the metabolism of sildenafil (4) and prolonging the duration of action of sildenafil. To our knowledge, PION has not been reported in association with sildenafil. We postulate that a sildenafil-induced decrease in blood pressure (6), together with vasculopathic risk factors and antihypertensive therapy, contributed to its development.

Daniel Hsien-Wen Su, FRCSEd
Singapore National Eye Centre
Singapore

Pei-San Ang, BSc (Pharm)
Centre For Drug Administration
Health Sciences Authority
Singapore

Sharon Lee-Choon Tow, FRCSEd
Singapore National Eye Centre
Singapore

sharon.towl.c@snec.com.sg

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Stepwise Decline in Visual Field After Serial Sildenafil Use

Phosphodiesterase type-5 (PDE-5) inhibitors such as sildenafil, tadalafil, and vardenafil are widely prescribed in the treatment of erectile dysfunction. Previous reports (1–4) have described a temporal association of PDE-5 inhibitor use with nonarteritic anterior ischemic optic neuropathy (NAION). We report a patient who suffered three episodes of permanent visual field loss, each following closely after ingestion of 100 mg sildenafil.

A 63-year-old Caucasian man with erectile dysfunction had used 25 mg sildenafil episodically for 5 years without incident. He had essential hypertension treated with amlodipine. Two weeks after an uncomplicated prostatectomy for prostate cancer, he had attempted unsuccessfully to achieve erection using a single dose of 100 mg sildenafil. The next day, he noted “cloudiness” and a dark brown color in the inferior field of his left eye.

Ophthalmologic examination elsewhere 17 days after the 100 mg sildenafil dose disclosed a best-corrected visual acuity of 20/20 in both eyes. A left afferent pupillary defect was present. An inferior nerve fiber bundle visual field defect was present in the left eye. The visual field in the right eye was normal (Fig. 1). Ophthalmoscopic examination showed superior and nasal edema of the left optic disc with flame hemorrhages consistent with NAION. Results of the remainder of his ophthalmologic examination were normal, including nontender temporal arteries with intact pulsation and a normal sedimentation rate.

Over the next 14 days, he took two additional 100 mg doses of sildenafil. Within 24 hours of each dosing, he noted stepwise enlargement of the inferior visual field defect of the left eye. With the first decline, the defect expanded to cover the “lower 50%” of the left visual field. This defect remained stable until the next dosing when it expanded to involve his “line of sight.” At that point, visual acuity in the left eye was documented at 20/40, but no formal visual field test was performed. He stopped using all PDE-5 inhibitors and was able to achieve erections using local injections of alprostadil. He reported no further visual field loss.

Six months after stopping the use of sildenafil, he requested a neuro-ophthalmologic evaluation. Best-corrected visual acuity was 20/20 in the right eye and 20/40 in the left eye. An afferent pupillary defect and dyschromatopsia were present in the left eye. Automated visual field analysis showed a full field in the right eye. In the left eye, there was an inferior nerve fiber bundle defect comparable to that seen in Figure 1 but with extension into the fixational region (Fig. 2). Ophthalmoscopic examination showed a normal right optic disc (cup-to-disc ratio of 0.1) and a pale left optic disc. The remainder of the neuro-ophthalmologic examination was normal. Results of blood testing for the mitochondrial DNA mutations of Leber hereditary optic neuropathy were negative.

Previous reports have described NAION with symptom onset between 30 minutes and 36 hours after PDE-5 inhibitor ingestion (1–4). In the series of Pomeranz and Bhavsar (3), as in other published series (1,2,4), patients have had a high prevalence of established risk factors for NAION, including a “disc at risk” and arteriosclerotic risk factors (hypertension, hyperlipidemia, and coronary artery disease). Similar characteristics were noted among patients with NAION after tadalafil ingestion (5,6). Because of these confounders, many have questioned whether the PDE-5 inhibitor use and the subsequent NAION were unrelated.

Hence, rechallenge cases are important. Bollinger and Lee (5) described a case in which the patient experienced transient visual field loss within 2 hours of the first four doses of tadalafil. After the fifth dose, the patient developed unilateral NAION with persistent visual field loss. Pomeranz and Bhavsar (3) described a case of bilateral sequential NAION with continued use of sildenafil after the first occurrence of NAION.

Our patient is notable in having had a three-step decline in visual field after sequential use of sildenafil. We acknowledge that the visual field loss in NAION can expand spontaneously over several weeks after initial symptoms (7). Yet in our patient, each decline occurred within 24 hours of ingesting the agent and visual field analysis.
Letters to the Editor


FIG. 2. Octopus visual fields performed 6 months after 100 mg sildenafil use. They show extension of the nerve fiber bundle defect of Figure 1 into the fixational area.

documented a worsening. Accordingly, it is tempting to consider that sildenafil played a precipitating role.

As with patients in other reports, our patient did have risk factors for spontaneous NAION (hyperopia and a small cup-to-disc ratio). And as for the other reported patients, he had used sildenafil for years without developing NAION. But the dose of sildenafil used just before stepwise visual field decline attributed to NAION events was four times larger than his usual dosage. Akash et al (1) have also reported the development of NAION shortly after excessive sildenafil dosage of 200 mg a few hours earlier. The patient had used sildenafil previously in a dose of 100 mg two to three times a week over a few months without side effects. It has been suggested that patients with a history of NAION avoid future PDE-5 inhibitor ingestion. This report supports such a recommendation.

Susan Pepin, MD
Ian Pitha-Rowe, MD, PhD
Dartmouth Medical School
Hanover, New Hampshire
Susan.M.Pepin@Hitchcock.org

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Intravitreal Triamcinolone for Nonarteritic Anterior Ischemic Optic Neuropathy

In a recent article in this journal, Kaderli et al (1) reported improved visual acuity outcomes and faster resolution of optic disc edema (ODE) in four eyes with nonarteritic anterior ischemic optic neuropathy (NAION) treated with intravitreal triamcinolone compared with six untreated eyes.

It is essential to place their findings in proper historical perspective. Nearly four decades ago, Foulds (2) stated that “A temporary ischaemia may lead to oedema of the nerve head which in turn further impedes capillary circulation leading to further anoxia so setting up a vicious circle.” He (3) later stated that “Because increased capillary permeability appears to be an important factor in the development of a full picture of ischaemic optic neuropathy, we have recently been treating such patients with large doses of systemic steroids.” He (3) reported his experience of systemic corticosteroid therapy in 24 patients with NAION showing significant visual acuity improvement compared with untreated patients. In 1974, I (4) reported visual acuity improvement in 75% of eight treated eyes with NAION compared with visual acuity improvement in 17% of six untreated eyes. By way of explanation, I (4) proposed that “Reduction of oedema by the steroid would relieve the pressure on the disc capillaries and restore some circulation in the vessels of the optic nerve head.” We (5) also recently reported the effect of systemic corticosteroid therapy on ODE in a prospective study of 343 treated eyes with NAION and 380 untreated eyes with NAION; there was significantly (P = 0.0006) faster resolution of ODE in the treated group, independent of severity of initial visual field or visual acuity loss.

The study of Kaderli et al (1) has some notable flaws:
1. Their exclusion criterion was a visual acuity of better than 20/200. According to our study (6), that would
exclude 75% of eyes with NAION one is likely to see. In our study (6), as well as in the Optic Nerve Sheath Decompression Study (7), only eyes with visual acuity of better than 20/70 were excluded from evaluation of visual acuity improvement or deterioration. Moreover, our natural history study (6) of visual outcome in NAION showed spontaneous visual acuity improvement in 41% (similar to that reported by the Optic Nerve Sheath Decompression Study (7)), and visual field improvement in 26% (6).

2. In their study (1), although visual acuity improved in the treated eyes, no change in visual field defects was observed. We have found in studies on NAION and arteritic anterior ischemic optic neuropathy (AION) (2,3) that apparent visual acuity improvement without visual field improvement is due to eccentric fixation and does not represent a genuine improvement. Such patients evidently learn to read the visual acuity test chart better by looking around. This phenomenon applies particularly to eyes with altitudinal visual field defects or other defects that abut on fixation. In the series of Kaderli et al (1), all treated and untreated eyes had altitudinal visual field defects; eccentric fixation may therefore explain visual acuity improvement without visual field improvement.

3. The treated eyes were masked neither to the investigators nor to the patients, a study design that has the potential of introducing visual acuity testing bias. Moreover, the study is based on treatment of only four eyes.

In light of these limitations, one must accept their results with reservations.

Sohan Singh Hayreh, MD, PhD, DSc, FRCS, FRCOphth
Department of Ophthalmology and Visual Sciences
University of Iowa
Iowa City, Iowa
sohan-hayreh@uiowa.edu

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Reply:

We thank Dr Hayreh for his comments on our article (1) and agree that the background and rationale of our study are more complete with the historical perspective he has contributed. Our replies to his main points are as follows:

1. Exclusion of eyes with visual acuity better than 20/200 in our study “would exclude 75% of the eyes with nonarteritic anterior ischemic optic neuropathy (NAION)” (2). Considering the possible complications of intravitreal triamcinolone and the lack of convincing evidence for efficacy of intravitreal triamcinolone in this disease process, we preferred to include only the most severely affected eyes.

2. The “apparent visual acuity improvement without visual field improvement is due to eccentric fixation and does not represent a genuine improvement,” a phenomenon he has noted in cases of NAION and arteritic anterior ischemic optic neuropathy (AION) (2,3) We emphasize the unusually rapid reduction in optic disc edema in our triamcinolone-injected eyes. In their series of nine patients with radiation papillopathy who were receiving 4 mg intravitreal triamcinolone acetamide, Shields et al (4) reported that signs of optic neuropathy such as hyperemia and edema resolved within 1 month. The overall median (range) time to spontaneous resolution of optic disc edema from the onset of visual loss in NAION was 7.9 (5.8–11.4) weeks in the study of Hayreh and Zimmerman (5). These data suggest that intravitreal triamcinolone leads to faster recovery of optic disc edema than is seen in untreated NAION.

Whether intravitreal triamcinolone improves a reversible component of ischemic injury in NAION remains unclear. Visual field measurement may not be sensitive enough to detect a small amount of recovery of retinal ganglion cell axon function. More objective and sensitive methods for nerve fiber analysis such as Heidelberg retina tomography (6), optic coherence tomography (7), and scanning laser polarimetry (8) may help detect and compare the axonal loss in patients with treated and untreated NAION.

As we stated in our report (1), “The interpretation of our results is cautioned by the small sample size.
Randomized studies with larger sample sizes are needed to show safety and efficacy.”

Berkant Kaderli, MD
Remzi Avcı, MD, MD
Ali Yucel, MD
Department of Ophthalmology
Uludag University School of Medicine
Bursa, Turkey

Kazim Guler, MD
Focus Laser Eye Center
Bursa, Turkey

Oner Gelisken, MD
Department of Ophthalmology
Uludag University School of Medicine
Bursa, Turkey
drkaderli@yahoo.com

REFERENCES

Animal Model for Nonarteritic Anterior Ischemic Optic Neuropathy

I want to comment on the issue of an animal model for nonarteritic anterior ischemic optic neuropathy (NAION) discussed by Kelman (1) in a recent editorial in this journal.

According to Bernstein et al (2), the animal model was produced by “argon laser light or frequency-doubling yttrium-aluminum garnet laser (YAG)” application to the “intraretinal portion” of the optic nerve (the surface nerve fiber layer of the optic nerve head). To determine the validity of this animal model of NAION, one must consider the fundamental issues related to the blood supply of the optic nerve head (ONH) and the pathogenesis of NAION.

It is well established now that the ONH is supplied by two independent arterial sources. Its surface nerve fiber layer is supplied by the central retinal artery circulation and its deeper part by the posterior ciliary artery circulation (3,4).

NAION is due to vascular insufficiency in the deeper part of the ONH supplied by the posterior ciliary artery circulation only and not of the central retinal arterial circulation. Bernstein et al (2) produced thermal and tissue disruption lesions in the surface nerve fiber layer of the ONH (supplied by the central retinal artery circulation) and did not selectively produce hypoxia of the relevant deeper part of the ONH. Thus, the optic nerve damage produced in their animal model is somewhat akin to that produced by central retinal artery occlusion(5) and not by posterior ciliary artery vascular insufficiency.

Bernstein et al (2) claim that they produced “thrombosis” of the superficial layer of the ONH (supplied by the central retinal artery circulation). In fact, in addition to producing thrombosis, their method produced massive tissue damage in that layer as well. The argon laser produces generalized thermal injury at the site of application, and the YAG laser produces widespread generalized tissue damage both by heat and tissue disruption (like the explosion of a minibomb). Thus, in their model, there is generalized tissue damage of capillaries, axons, and glial tissue in the superficial nerve fiber layer of the ONH.

In NAION, by contrast, the ONH damage is caused by hypoxia of its deeper part. This is wholly different from the generalized thermal and tissue disruption injuries caused by argon and YAG lasers in the superficial nerve fiber layer. There is now ample evidence to support the concept of hypoxia causing the ONH damage in NAION (6,7). Hypoxic damage is most often produced by abnormal nocturnal arterial hypotension in persons with other risk factors (6,7). Vascular insufficiency in the ONH caused by abnormal nocturnal arterial hypotension is a transient phenomenon that does not always produce irreversible severe axonal damage. The proof is that in NAION there is a spontaneous visual improvement (8,9). In contrast, argon and YAG lasers produce thermal damage to the capillaries, axons, and other tissues in the ONH, and the YAG laser is highly disruptive, with irreversible, generalized, marked damage to all tissues in the superficial nerve fiber layer. Therefore, this animal model totally lacks the pathogenetic basis of NAION and...
is unsuitable as an experimental model for studying this condition.

**Sohan Singh Hayreh, MD, PhD, DSc, FRCS, FRCOphth**
Department of Ophthalmology and Visual Sciences
University of Iowa
Iowa City, Iowa
sohan-hayreh@uiowa.edu

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8. Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. *JAMA* 1995;273:625–32.


**Reply:**

We want to reply to Dr. Hayreh’s comments on the validity of our rat and mouse models for nonarteritic anterior ischemic optic neuropathy (NAION) (1,2). Dr. Hayreh’s suggested explanations for the effects of the model are neither technically nor physiologically correct. Although we have great respect for Dr. Hayreh’s previous work, he either misunderstands or is unfamiliar with the mechanisms of light activated-rose bengal photothermolysis and ignores the characteristics of the newer medical laser types and their effects in the power ranges used in our studies. In addition, he apparently has misinterpreted the site of the lesion induced in our model and bases his conclusions on his previous work. In fact, these conclusions can easily be refuted by a careful review of our published work (1–3) and of many other primary references (4–8), ranging from 1954 through the present day.

The rose bengal photoactivation model of NAION uses superoxide radical formation, not thermal energy. Rapidly degrading (10^-12 seconds) superoxide radical molecules damage the vascular endothelium, resulting in platelet-fibrin thrombosis of the vessels. Multiple reports (4–7) describe this process and its use in the retina as well as in other systems. The development of intravascular platelet-fibrin thrombi with this technique are well documented and are produced without using laser-generated coherent light. In producing our model, we used 514 nm (argon green) or 532 nm frequency-doubled yttrium-aluminum-garnet (fd-YAG) (green light) lasers because they effectively overlap and illuminate the capillaries supplying the anterior optic nerve without causing significant damage to surrounding tissue. Unlike the classical YAG laser (1,065 nm) that used destructive interference of two beams (what Dr. Hayreh describes as a “minibomb”), the fd-YAG laser is similar to an argon laser and has generally replaced the argon laser for the treatment of most ocular disorders.

We do not dispute the fact that high levels of laser power exposure coupled to large spot sizes can result in indiscriminate tissue necrosis and poorly discriminated deeper retinal damage (9), and we were mindful of the possibility of laser-induced thermal damage when we designed our studies. Indeed, in our reports, we include data showing that the low laser power we used (50 mW) and appropriate spot size sufficient to only illuminate the nerve do not produce significant thermal tissue damage. The rat anterior ischemic optic neuropathy (AION) model lesion was shown to be nonthermal by multiple methods: 1) a lack of vascular damage with laser exposure alone (sham treatment), which was determined by using India ink vascular mapping analysis (8) (1), revealing that only dye-coupled laser activation results in isolated optic nerve capillary loss, with continued patency of the larger central retinal vasculature (1); 2) no target neuron (retinal ganglion cell) loss with laser exposure alone (3); and 3) photo-induction-isolated retinal ganglion cell loss without disruption of deeper retinal cell layers. The above effects do not indicate any indiscriminate tissue damage induced by thermal necrosis (1).

Although photothermolysis of the optic nerve surface capillaries clearly occurs in our model, a more careful analysis of our data (2) also shows that there is a deeper focal effect in the retro-ocular optic nerve (the rodent does not have a lamina cribrosa), similar in depth to that clinically seen in the only early clinical case available (10). Dr. Hayreh’s statement that “...NAION is due to vascular insufficiency in the deeper part of the ONH supplied by the posterior ciliary artery only” is also disputable. Dr. Hayreh provides no cited evidence for this statement, although there is much debate about the role of nocturnal hypotension in NAION. Unlike arteritic AION, for which Dr. Hayreh is due considerable credit, we are unaware of
any cases of NAION that have been demonstrated to be due to vascular insufficiency in any specific bed.

We have never claimed that our rat AION model is identical to human NAION. Rather, we state that it has considerable similarities and that the responses of model-treated animals are likely to be similar. The rat AION model is a tool that enables us to study individual events underlying the response of retinal ganglion cell neurons, as well as cellular events and responses of the vasculature and glial cells of the optic nerve. This tool can provide answers to questions about isolated optic nerve ischemia that have not and cannot be answered by other currently available methods. In short, the model that we have developed is and remains a valuable method for analysis of the effects of isolated optic nerve ischemia on the retina, optic nerve, and individual cell types. The model is likely to be useful for evaluation of neuroprotective strategies focused on treatment of isolated retinal ganglion cell (RGC) ischemic disease.

Steven L. Bernstein, MD, PhD
Departments of Ophthalmology, Anatomy and Neurobiology, and Genetics
University of Maryland School of Medicine
Baltimore, Maryland

Shalom E. Kelman, MD
Department of Ophthalmology
University of Maryland School of Medicine
Baltimore, Maryland

Neil R. Miller, MD
Departments of Ophthalmology, Neurology, and Neurosurgery
Johns Hopkins Medical Institutions
Baltimore, Maryland

REFERENCES

I Am a Retinal Migraineur

Two recent publications in this journal (1,2) discussing retinal migraine have prompted me to report my personal history of multiple occurrences that I am calling “retinal migraine.”

I am now a 71-year-old ophthalmologist with a 55-year history of recurrent—often intense—unilateral headaches, lasting as long as 12 hours, frequently preceded by a short interval of enhanced sensitivity to light or sound and sometimes accompanied by nausea. The episodes are free of other visual disturbances.

I experienced my first homonymous scintillating scotoma without accompanying headache at age 25 as a small visual defect near central fixation. This developed into a fortification spectrum of silvery parallel zigzag lines that expanded peripherally, eventually disappearing in the nonpaired homonymous field after 15-20 minutes. Some of the lines had red and blue colored borders. Similar episodes have occurred up to the present time at intervals from one or two per week to one every few months. The scotomas have occurred in either hemifield but mostly on the right. They have uncommonly been associated with or followed by headache.

At age 56, I noted for the first time an unequivocally monocular absolute scotoma in the left inferior nasal field of the left eye near the point of fixation. It lasted 10 minutes, and I recorded it on an Amsler grid (Fig. 1A). Approximately 1 minute before the scotoma disappeared, the peripheral part of the scotoma began to contract, and the residual scotoma faded completely without any residual visual defect and without any accompanying systemic or neurologic manifestations. My pulse rate remained regular during the episode. Although I experienced some anxiety at the thought that this might represent an impending stroke, its short duration led to a self-diagnosis of retinal migraine. Nearly identical monocular events occurred in May 1993, December 1993, May 1999, May 2000, May 2003, November 2003, July 2003, December 2003, February 2005, December 2006, and February 2007. I have reproduced the scotomas of some of these events (Fig. 1B-D). In each event, the scotoma remained relatively stable for approximately 10 minutes and then receded over
1 minute. In February 2005, while I was driving an automobile, I experienced the only monocular event that involved my right eye.

At the beginning of the May 2003 event, I instilled tropicamide into my affected left eye. Within 6–7 minutes, I was examined by a retinal specialist working in an adjacent office, who found no evidence of retinal vasospasm, embolic phenomena, or other abnormalities. The scotoma persisted for approximately 2 minutes after the fundus examination.

The December 2003 monocular scotoma is thus far the only one with an accompanying headache (preceding the scotoma and lasting about 2 hours). The homonymous scintillating scotomas have continued but never during or even close to the time of the monocular events.

I have always been in good health, have had normal blood pressure and serum lipid levels, and have had no systemic or neurologic abnormalities requiring medications. None of the binocular or monocular visual events has had a temporal relationship to any of the commonly cited triggering events such as stress, fatigue, or ingestion of caffeine, alcohol, or spicy foods.

Winterkorn (2) has called “retinal migraine” an oxymoron because the retina does not appear to experience spreading depression. Whatever you may wish to call these monocular visual events, they have been stereotypic, short-lived, isolated, life-long, benign, and present in a patient who has experienced migraine events with typical visual aura at other times. Retinal migraine has been an accepted term included in the 2004 International Headache Society classification (3). The absence of recognized vasospasm during one of my episodes does not preclude the possibility of vasospasm as an etiology, but it does beg for an alternative explanation.

Dennis M. Robertson, MD
Department of Ophthalmology
Mayo Clinic
Rochester, Minnesota
robertson.dennis@mayo.edu

REFERENCES
Diagnostic Imaging: Brain

Scope: This book is divided into two parts. The first part organizes diagnoses according to general pathology and includes 10 sections covering congenital malformations, trauma, subarachnoid hemorrhage and aneurysms, stroke, vascular malformations, neoplasms and tumor-like lesions, primary and non-neoplastic cysts, infectious and demyelinating diseases, and finally, inherited and acquired toxic, metabolic, and degenerative diseases. The second part is organized by anatomic locations, including ventricles and cisterns, sella and pituitary, cerebellopontine angle, and skull, scalp, and meninges. The book contains 4,400 illustrations in 992 pages.

In the preface, chief author Anne Osborn states the rationale for the organization of the book: “We’ve become victims of our own success: we are getting better and better at imaging more and more stuff. This translates into an ever-increasing case load. Time is a luxury most of us don’t have. We need our information in an easily accessible format…. We don’t have time for extra words that don’t carry essential information so we don’t write them!” The authors’ “matter-of-fact” approach is followed rigorously in that each disorder is discussed over 4 pages. The discussion is divided into terminology, imaging findings, differential diagnosis, pathology, clinical issues, diagnostic checklist, selected references, and an imaging gallery, which in most cases includes 6 images (4 for the rare disorders). “Key Facts” and differential diagnosis are highlighted in boxes that contain short summaries of the entities and 4 images. The text is composed of bulleted statements that contribute to the uniformity of the book with hardly any stylistic difference between the different authors.

Strengths: The book provides a huge amount of information on hundreds of diagnostic entities from the most common (meningioma and multiple sclerosis) to the rarest (cerebellar hemorrhage). The information is not limited to neuroradiology; there is up-to-date information on pathology, physiology, epidemiology, and clinical features with the latest references in each area. The images themselves are impressive and are derived from advanced techniques such as MR spectroscopy, diffusion weighting, MR perfusion, noninvasive angiography, and digital subtraction catheter-based angiography. The imaging findings section includes recommendations for the best imaging tool and protocols for best yield. The magnificent color illustrations done by James A. Cooper convey the essentials of diagnosis, and provide correlation between the gross pathology and the CT and MR images.

Weaknesses: The format of bulleted statements is sometimes hard to follow and the overuse of abbreviations distracts the flow of reading. The reader is forced to turn back and forth from the text to the lists of abbreviations placed in the beginning of the book and on the first page of each section. In addition, the organization is cumbersome, with complicated sets of numbers assigned to entries according to their location in the book. A more traditional method would have been easier to follow.

Recommended Audience: This is an invaluable source of information for the neuroradiology, neuropathology, neurology, and neurosurgery communities.

Critical Appraisal: Although this relatively compact volume makes you miss an “old-fashioned” prose textbook such as Osborn’s “Diagnostic Neuroradiology,” it may be the best and only way to compress an enormous amount of information and rich imaging gallery into a single textbook.

Iris Ben-Bassat Mizrachi, MD
Goldschleger Eye Institute
Sheba Medical Center
Ramat Gan, Israel

The Neuro-Ophthalmology Survival Guide

Scope: This is a well-organized and well-illustrated text designed for the comprehensive ophthalmologist as a practical reference for addressing most neuro-ophthalmologic problems. It is organized in chapters by patient symptoms and signs. Chapters 2 through 12 cover topics such as “transient visual loss,” “double vision,” “seeing things,” and “unequal pupils.” Each of these chapters begins with several pages introducing the topic, an examination checklist, and a management flowchart. This provides a framework for the reader to organize an approach to the patient.
The remainder of each chapter provides more detailed information including suggested management of each entity on the differential diagnosis. Each chapter is designed to be used for quick reference while evaluating patients.

**Strengths:** The organization of the book by patient symptoms and signs makes it very easy for the reader to find relevant information. The text is comprehensive but succinct. The first chapter, “Twenty Neuro ‘Rules’ to Keep You out of Trouble,” is filled with important neuro-ophthalmology tidbits and should be read in its entirety by all ophthalmologists.

The many colored illustrations are helpful in amplifying the text.

**Weaknesses:** There are no major weaknesses. The authors do state that they wish to “…err on the side of caution in investigating and managing patients.” Nevertheless, occasionally the list of tests that “must” be obtained seems a bit much. For example, the following blood tests are considered mandatory in all patients with idiopathic intracranial hypertension: full blood count, glucose, electrolytes, liver function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), angiotensin-converting enzyme (ACE), and antinuclear antibodies (ANA). Perhaps this approach is necessary for the ophthalmologist who has no neuro-ophthalmologist nearby, but there is a risk that any reader of this manuscript will simply order numerous tests when not necessary. Perhaps the word “must” is a bit too strong.

**Recommended Audience:** The authors state that this book is intended for the comprehensive ophthalmologist and clearly that group is well served. However, I think that comprehensive neurologists, residents, and junior neuro-ophthalmologists would also find this text very useful.

**Critical Appraisal:** This is an excellent, clinically relevant book essential to any physician who evaluates patients with potential neuro-ophthalmologic problems.

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**Eye on the Bayou: New Concepts in Glaucoma, Cataract and Neuro-Ophthalmology**


**Scope:** This book is a collection of the lectures and roundtable discussions from the 54th Annual Symposium of the New Orleans Academy of Ophthalmology. The book is divided into four main sections: neuro-ophthalmology, glaucoma, psychophysics, and anterior segment surgery. The target reader is the comprehensive ophthalmologist. Each subspecialty section contains the text of several lectures and roundtable discussions designed to address questions introduced by the preceding lectures. The roundtable panel consists of several “experts” who discuss their philosophy on difficult management issues.

The neuro-ophthalmology section contains transcripts of Andrew Lee’s excellent lectures on common mistakes when examining the neuro-ophthalmology patient, double vision and pupil involvement, an update on optic neuritis, and important points to communicate to patients with nonarteritic anterior ischemic optic neuropathy. Additionally, Lee discusses MRI, CT, and optical coherence tomography (OCT) indications in neuro-ophthalmology.

The second section includes lectures by Harry Quigley and Eve Higginbotham that cover epidemiological risk factors for glaucoma such as race and sex. This is followed by a discussion on low tension glaucoma and neuroprotection. Paul Palmberg critiques the commonly held belief that glaucoma structural damage precedes visual function loss. Finally, there are several succinct synopses of recent landmark glaucoma clinical trials (CNTGS, AGIS, EMGT, CIGTS, OHTS, and EGPS) followed by an interesting roundtable discussion critiquing these clinical trials.

The psychophysics section is primarily a series of lectures updating visual field testing with short wavelength automated perimetry (SWAP), frequency doubling technology (FDT), Swedish interactive thresholding algorithm (SITA), zippy estimation of sequential testing (ZEST), and tendency oriented perimetry (TOP). Additionally, there is a section on interpreting visual field loss in glaucoma and a roundtable discussion on detecting and monitoring glaucoma progression.

The final section consists of several lectures on anterior segment surgery and complications. The first lecture discusses the new disease entity “toxic anterior segment syndrome.” The remaining lectures are discussions of the basics of laser trabeculoplasty and clinical pearls on performing and managing trabeculectomy. Two roundtable discussions cover trabeculectomy skills by providing further pearls and suggestions for surgical infection prophylaxis.

**Strengths:** This book contains many useful diagnostic pearls relevant to comprehensive ophthalmologists. The text is easy to follow. The neuro-ophthalmology section is especially well done and practical. The roundtable discussions are insightful.
**Weaknesses:** The topics covered are relatively narrow. There is no index. If readers are not looking for updates on the specific topics, they may find the book focused on too little.

**Recommended Audience:** This book is aimed to the comprehensive ophthalmologist or specialist interested in updating knowledge in a different subspecialty. Additionally, individuals who attended the 54th Annual Symposium of the New Orleans Academy of Ophthalmology can use this book to review the material.

**Critical Appraisal:** This book provides a practical, succinct update on narrow but important topics to the practicing comprehensive ophthalmologist or resident physician.

Christopher Thiagarajah, MD
Karl Golnik, MD, MEd
University of Cincinnati
and the Cincinnati Eye Institute
Cincinnati, Ohio

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**Neuroanatomy: An Illustrated Colour Text, 3rd Edition**

A. R. Crossman, PhD, DSc, and David Neary, MD, FRCP.

**Scope:** This is an introduction to the anatomy of the central and peripheral nervous system broken up into 17 chapters in 186 pages. The text is supplemented with diagrams and photographs of pathologic specimens.

The first chapter includes an overview of the embryology and anatomy of the central nervous system. In this chapter and subsequent ones, little inserts provide descriptions of developmental anomalies and boxes emphasize important clinical messages. Simplified diagrams emphasize clinical points. Chapter 15 consists of a description of the visual system with a very basic presentation of ocular anatomy and the visual pathways.

This edition contains a final chapter on problem solving, consisting of 10 case vignettes associated with questions and answers. In addition, there is a glossary of terms, which makes it easy to find definitions.

**Strengths:** This is an extremely well-illustrated text introducing an increasingly detailed and difficult subject. The diagrams are simple and straightforward; they synthesize a very complex subject into a more manageable explanation. The widespread use of diagrams and illustrations and summary inserts is extremely helpful.

**Weaknesses:** This is not a sophisticated reference text, nor does it intend to be. It does not include corresponding imaging studies that might make it even more clinically relevant to a student making the transition between anatomy and clinical diagnosis.

**Recommended Audience:** The authors clearly target medical students being introduced to neuroanatomy.

**Critical Appraisal:** This book is a major improvement over its predecessors of 40 years ago. The use of diagrams, color illustrations, and early clinical implications is essential to its success. Although it is unlikely to be useful to those in the practice of neuro-ophthalmology, those who want to know how our students are being introduced to neuroanatomy will find it helpful.

Steven A. Newman, MD
Department of Ophthalmology
University of Virginia
Charlottesville, Virginia

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**Interactive Atlas of the Human Brain**

Robert E. Kingsley, PhD, and Robert D. Kingsley, MFA.

**Scope:** This is a CD-ROM designed to teach neuroanatomy to students, clinicians, and scientists. It contains 4,381 images that depict neuroanatomy in a dynamic, interactive format.

The brain can be viewed in various formats including as anatomical dissections and various MR imaging sequences. Additionally, the brain can be viewed in sagittal, axial, and coronal planes. The images can be viewed with all labels in place, with select labels, or with unnamed lines as in quiz format.

**Strengths:** This CD-ROM allows one to study anatomical sections and correlate them with MR imaging. It facilitates the development of a three-dimensional understanding of neuroanatomy that can be difficult to achieve through the pages of a book alone. The images are generally of high quality.

**Weaknesses:** Although the overall format of the atlas is user friendly, it would be ideal to be able to click on a structure of the brain and have the label and/or the pointing line appear.

**Recommended Audience:** This CD-ROM is effectively targeted as a resource for any student of neuroanatomy and
will also be useful for resident trainees, scientists, and clinicians dealing with the human brain.

Critical Appraisal: This atlas should prove to be a wonderful tool for all those interested in neuroanatomy. It will undoubtedly be incorporated into the training of neurosurgical residents at our program.

John A. Jane, Sr., MD, PhD, FRCS(C)
Department of Neurosurgery
University of Virginia Health System
Charlottesville, Virginia

Stroke


Scope: This is a primer aimed at internists and non-neurologists with the hope of familiarizing them with the rudimentary aspects of stroke—its causes, presentations, evaluation, and treatment. With few exceptions, the chapters are written by faculty members of The Johns Hopkins University Medical School and the book is edited by two of the leaders in stroke neurology at that institution.

Strengths: The book is very well organized and covers the practical issues in the care of stroke patients. In general, the chapters present material in a straightforward, easily understood style. Case examples, key points, useful tables, general principles, and guides to treatment are sprinkled generously throughout. Illustrations are relatively sparse but well chosen. The book is very user-friendly to those inexperienced in the topic. The authors of the chapters are clearly knowledgeable about their respective fields and effectively convey the necessary information. I could not find any didactic points to quarrel with, and all the chapters are of very good quality.

Weaknesses: The information is relatively basic for neurologists, especially those specialized in stroke. There is little about neuro-ophthalmology.

Critical Appraisal: This is a very good book for internists and neurologists who do not specialize in stroke. Useful practical information and guides are packed into a relatively small, handy book. The book is very user friendly and up-to-date.

Louis R. Caplan, MD
Department of Neurology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Fragments of Neurological History


Scope: This book is a compendium (and amplification) of “space fillers” that appeared one-by-one over the past several decades in the Journal of Neurology, Neurosurgery, and Psychiatry (JNPP). The author was asked to compose “jottings” of biographical details and medical contributions of our forebears in medicine, mostly neurologists, and mostly European. You will encounter the “big names” of eponymic fame—Virchow, Broca, Westphal, Ménière, Binswanger, Brown-Sequard, and many, many others—with their delicious idiosyncrasies described in 135 short essays that make for wonderful bedtime reading.

Strengths: If you want to find out where the titans behind the syndromes came from, who promoted them and who impeded their professional progress, how they philandered, whose ideas they plundered, and how they died, then you will love this book. It is like reading the gossip column, but several hundred years later. Apart from unearthing gossip, the author has done a fine job of setting the historical record straight. For example, he points out that Sir Charles Bell (by the way, not the other Scottish physician Joseph Bell, who was the model for Sir Arthur Conan Doyle’s Sherlock Holmes) described a facial palsy that followed trauma, not the idiopathic (postviral) version we now call “Bell’s palsy.” There are five wonderful essays on Duane, Marcus Gunn, Holmes, Adie, Bernard, and Horner.

Weaknesses: Just when you are warmed up and ready to learn about the juicy details, you are often disappointed that the author could not come up with much beyond standard demographics. By way of explanation, the author quotes William Munk as saying that “the more successful a physician is, the less is there to meet observation or to court publicity, and the less material, therefore, for biography.” That is true for many of our heroes of yesteryear, but fortunately not all.

Recommended Audience: This book will be especially enjoyable for history buffs, particularly those with an interest in quirky biographical information about the figures whose names we invoke every day.

Critical Appraisal: Notwithstanding the often trite biographical accounts, there is plenty of delightful material here. Nowhere else are you likely to find this variety of nifty information under one cover.

Jonathan D. Trobe, MD
Kellogg Eye Center
University of Michigan
Ann Arbor, Michigan
**Medicine in Quotations, 2nd Edition**


**Scope:** This is a collection of quotations about medicine and health assembled by two learned physicians from their own collection and contributions of others. The authors are estimable: Huth, an internist, was for 19 years the editor of Annals of Internal Medicine; Murray, a neurologist, is the former chair of the Board of Regents of the American College of Physicians and former dean of the medical school at Dalhousie University.

The quotations are grouped alphabetically by topic; quotations within each topic are listed chronologically. For example, under the topic “doctors,” there are 60 quotations, starting with Marcus Valerius Martialis in 50 AD and ending with Sherwin Nuland in 2001. As you move through the 4 pages on “doctors,” you will find quotations from Petrarch, Paracelsus, Montaigne, Molière, (Jonathan) Swift, (Alexander) Pope, (Benjamin) Franklin, Twain, (Oliver Wendell) Holmes, (Arthur Conan) Doyle, and (George Bernard) Shaw, to name the better known figures. There is also an index by authors.

**Strengths:** This is a marvelous resource for the rounds-person and after-dinner quipper. It is also an education in how wordsmiths have viewed medical topics through the course of time. In that way, it is a history of medicine—and it is marvelously illuminating. For example, Shaw is quoted as saying, “Even the fact that doctors themselves die of the very diseases they profess to cure passes unnoticed.” And Osler, who apparently said, “We doctors have always been a simple, trusting folk! Did we not believe Galen implicitly for fifteen hundred years?”

The only other source of this type is Familiar Medical Quotations (M. Strauss, editor), a book last published 50 years ago.

**Weaknesses:** This book is, after all, like a dictionary. You are unlikely to leaf through it; you would consult it for the apt occasion. And if you are not given to stuffing your speeches with quotations, you might never open it.

**Recommended Audience:** This book will appeal to anyone who loves language, history, or writing and especially to those who treasure the pithy quotation.

**Critical Appraisal:** With over 400 pages of material put together by two authors who clearly love language and history, this is the ultimate resource for medical sayings.

Jonathan D. Trobe, MD
Kellogg Eye Center
University of Michigan
Ann Arbor, Michigan
Jan Z. Winkelman, MD (1942–2007)

Nan Z. Winkelman, MD, died of Alzheimer disease on March 8, 2007, in Ann Arbor, Michigan, at the age of 64.

Jan was born in Detroit and attended Mumford High School where he excelled as a competitive swimmer and trumpeter. His father, a dermatologist, died when Jan was 8 years old and his mother became remarried to Isadore Winkelman, the youngest of several brothers who had emigrated to Michigan's Upper Peninsula as merchants. Isadore moved down to Detroit to found the first of many Winkelman women's clothing stores, which rapidly became the most popular source for fine articles at moderate prices. Jan recalled doing odd jobs at the stores with an idea that he might eventually join the family business. But after 4 years as an undergraduate at the University of Michigan, he decided to go to medical school, a second—but more realistic—choice than becoming a professional jazz musician.

At Washington University Medical School, he was exposed to the dynamic ophthalmology program and was smitten. After a year as a medical intern at Los Angeles County Hospital, he returned to Washington University for his ophthalmology residency and then a 1-year neuro-ophthalmology fellowship there under the tutelage of Ronald M. Burde, MD.

Following a 2-year stint in the Navy in Norfolk, Virginia, Jan returned to Ann Arbor in 1975 to join a community practice in partnership with Jerry Epstein, MD. John Henderson, MD, then the chairperson of the ophthalmology department at the University of Michigan, soon called on him to help the Michigan residents with their neuro-ophthalmology cases. His trainees remember that Jan was an astute diagnostician.

Eventually he moved into solo practice in affiliation with St. Joseph Mercy Hospital in Ann Arbor. His colleagues remember him as an innovative, dedicated, insightful, and selfless physician who did not balk at devoting a large part of his practice to brain-injured patients. In autobiographical notes, Jan said that “I really think that the traumatic brain injury service I ran was the most useful part of my career. It was an honor for me to help these people.”

When he was not practicing neuro-ophthalmology, he was playing the trumpet and raising funds for the local radio station known for its programming of jazz. He took up the study of the Italian language well past his midlife, spurred by fond recall of his junior year summer abroad when he lived with a peasant family in northern Italy. In 1991, he was rejuvenated in remarriage to Sarajane, with whom he melded two families, consisting of his three children, Michael, 39, an English professor, Larry, 37, a mechanical engineer, and Jeffrey, 31, a middle school teacher, and Sarajane's two children, Jill, 38, a social worker, and David, 34, an elementary school principal.

In the latter years of his medical practice, he returned to playing the trumpet. He began weekly lessons with Vincent York, a renowned brass player. Jan told me that he was never as nervous in the operating room as he was before his trumpet lesson. According to Sarajane, he never lost his excellent embouchure. He took his last lesson the week that he died.

Jonathan D. Trobe, MD
Kellogg Eye Center
University of Michigan
Ann Arbor, Michigan
Upcoming Meetings

March 8–March 13, 2008
34th North American Neuro-Ophthalmology Society (NANOS) Annual Meeting
Orlando, FL
http://www.nanosweb.org/meetings/index.htm
Contact: info@nanosweb.org

April 2–April 6, 2008
American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Washington, DC
http://www.aapos.org
Contact: aapos@aao.org

April 12–April 19, 2008
60th Annual Meeting of the American Academy of Neurology (AAN)
Chicago, IL
http://aan.aan.com/
Contact: memberservices@aann.com

April 26–May 1, 2008
76th Annual Meeting of the American Society of Neuroradiology (ASNR)
New Orleans, LA
Contact: meetings@asnr.org

April 27–May 1, 2008
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Boston, MA
http://www.arvo.org
Contact: arvo@arvo.org

May 13–May 16, 2008
European Stroke Conference
Nice, France
http://www.eurostroke.org/esc_congresses.htm
Contact: hennrici@eurostroke.cu

May 15–May 17, 2008
Asia Neuro-Ophthalmology Society (ASNOS)
Taipei, Taiwan
http://www.asnos2008.tw/
Contact: oph4@oph.org.tw

May 18–May 20, 2008
Society of Neurological Surgeons Annual Meeting
Madison, WI
http://www.societyns.org/meeting/index.html

May 21–May 24, 2008
18th International Visual Field and Imaging Symposium
(International Perimetric Society)
Nara City, Japan
http://www.congre.co.jp/ips2008/
Contact: ips2008@congre.co.jp

June 1–June 5, 2008
46th Annual Meeting of the American Society of Neuroradiology (ASNR)
New Orleans, LA
Contact: meetings@asnr.org

June 7–June 11, 2008
18th Meeting of the European Neurological Society
Nice, France
http://www.akm.ch/ens2008
Contact: info@akm.ch

June 7–June 12, 2008
International Neuro-Ophthalmology Society (INOS)
Napa, CA
Contact: info@inos2008.org

June 11–June 14, 2008
Canadian Ophthalmological Society Annual Meeting
Whistler, BC
http://www.eyesite.ca/english/calendar.htm
Contact: am@eyesite.ca

June 17–June 20, 2008
Canadian Neurological Sciences Federation 43rd Annual Congress
Victoria, British Columbia, Canada
http://www.cnfsociety.org/general_information_congress.html
Contact: jroy@advance-group.com

June 24–June 27, 2008
XIX Symposium of the International Society on Metabolic Eye Disease
Guangzhou, China
Contact: optoedcorp@aol.com
June 26–June 29, 2008
50th Annual Scientific Meeting of the American Headache Society
Boston, MA
http://www.americanheadachesociety.org
Contact: ahsmtgs@talley.com

June 28–July 2, 2008
World Ophthalmology Congress
XXXI International Congress of Ophthalmology
XIII Congress of the Chinese Ophthalmological Society
XXIII Congress of Asia-Pacific Academy of Ophthalmology
XX Hong Kong Ophthalmological Symposium
Hong Kong
http://www.woc2008hongkong.org/
Contact: info@woc2008hongkong.org

July 9–July 11, 2008
31st Annual Meeting of the Japanese Neuroscience Society
Tokyo, Japan
Contact: neurosci2008@congre.co.jp

July 12–July 16, 2008
6th Forum of European Neuroscience Societies FENS
Geneva, Switzerland
http://fens2008.neurosciences.asso.fr/
Contact: online form only

Aug. 23–Aug. 26, 2008
12th Congress of the European Federation of Neurological Societies (EFNS)
Madrid, Spain
http://efns2008.efns.org/
Contact: efns08@kenes.com

Sept. 20–Sept. 25, 2008
Congress of Neurological Surgeons 58th Annual Meeting
Orlando, FL
http://www.neurosurgeon.org/meetings/meetingsites.asp
Contact: info@1cns.org

Sept. 21–Sept. 24, 2008
133rd Annual Meeting of the American Neurological Association
Salt Lake City, UT
http://www.anneuroa.org
Contact: julieratzloff@llmsi.com

XVIII International Congress for Eye Research (ICER)
Beijing, China
http://www.chinamed.com.cn/2008icer
Contact: gejian@mail.sysu.edu.cn

Sept. 24–Sept. 27, 2008
6th World Stroke Congress
Vienna, Austria
http://www.kenes.com/stroke2008/
Contact: stroke2008@kenes.com

European Association for Vision and Eye Research (EVER) Annual Congress
Portorož, Slovenia
Contact: ever@ever.be

Nov. 8–Nov. 11, 2008
Annual Meeting of the American Academy of Ophthalmology (AAO)
Joint Meeting with the European Society of Ophthalmology (SOE)
Atlanta, GA
http://www.aaoo.org/meetings/annual_meeting/atlanta.cfm
Contact: meetings@aaoo.org

Nov. 15–Nov. 19, 2008
38th Annual Meeting of the Society for Neuroscience
Washington, DC
http://www.sfh.org/index.cfm?pagename=annualmeeting
Contact: info@sfh.org

Feb. 21–Feb. 26, 2009
35th North American Neuro-Ophtalmology Society (NANOS) Annual Meeting
Lake Tahoe, CA
http://www.nanosweb.org/meetings/index.htm
Contact: info@nanosweb.org

32nd Annual Meeting of the American Society of Neuroimaging
Lake Buena Vista, FL
http://asnweb.org
Contact: asna@llmsi.com

June 17–June 20, 2009
European Neuro-Ophtalmology Society (EUNOS)
Luebeck, Germany
http://www.eunos2009.org
Contact: detlef.koempf@neuro.uni-luebeck.de

19th World Congress of Neurology
Bangkok, Thailand
http://www.wfnneurology.org/
Contact: WFNLondon@aol.com