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Manuscripts should be submitted to Jonathan D. Trobe, MD, Editor-in-Chief, Journal of Neuro-Ophthalmology, Kellogg Eye Center, Department of Ophthalmology, 1000 Wall Street, Ann Arbor, MI 48105.
Treat Early, but Treat Hard: Interferon-β Dose Makes a Difference

Daniel D. Mikol, MD, PhD

The manuscripts by Rudick (pp 279–291) and Galetta (pp 292–295) in this issue of the journal reinforce the benefits of early treatment of MS and highlight new therapeutic approaches on the horizon. In an era when treatment options for multiple sclerosis are likely to continue increasing, we must try to make sense of already available therapies.

Four disease-modifying drugs have been approved for use in the United States: glatiramer acetate (Copaxone®, Teva Neuroscience), mitoxantrone (Novantrone®, Immunex), and two interferon (IFN)β products IFNβ-1a, (Avonex®, Biogen) and IFNβ-1b (Betaseron®, Berlex-Schering AG). Another IFNβ-1a (Rebif®, Serono) already available outside the United States, is likely to be released here in 2002. IFNβ-1b was the first drug approved for the treatment of MS in 1993, and IFNβs remain the stronghold of disease-modifying therapy. All IFNβs have a positive impact on clinical and MRI parameters of disease activity. While the three IFNβs are nearly identical structurally (Avonex® and Rebif® are identical), they differ in composition, route of injection, and, most importantly, dose and frequency of injection. In terms of weekly biologic activity, Avonex® (30 µg) is 4–5-fold lower than either Betaseron® (875 µg weekly) or high-dose Rebif® (132 µg), which are comparable.

EXPERIMENTAL EVIDENCE

For years, experimental studies have suggested that IFNβ efficacy is dose-dependent. A number of biologic response markers induced by IFNβ, such as serum neopterin and the human Mx protein, respond in a dose-dependent fashion, irrespective of whether the agents are administered intramuscularly (IM) or subcutaneously (SQ) (1). IFNβ-induced changes last less than a week, suggesting that injections should be given more than once a week. In vitro data indicate that IFNβ dose-dependently inhibits T-cell activation (2) and transendothelial migration (3, 4), and dose-dependently modulates the expression of several immune cell mediators such as interleukin-10 (5–8). Further, IFN-γ-induced expression of major histocompatibility class II molecules is suppressed in a dose-dependent manner by IFNβ-1a (9). These different dose-dependent actions are all likely to have beneficial effects on the immunologic processes at play in MS patients. In EAE, an animal model of MS, IFNβ has dose-dependent effects on relapse rate, mortality rate, neurologic function and lesion size (10, 11).

DOSE, SIZE, AND FREQUENCY

Pharmacokinetic studies have shown that standard Betaseron® dosing results in a more consistently elevated and sustained biologic response than standard Avonex® dosing. Betaseron® provides sustained increases in IFNβ-induced biologic markers over the course of a week, whereas Avonex® shows a decline in parameters on the fifth day (12). Rothuizen et al. (13) compared the levels of inflammatory response mediators to IFNβ-1a given once-weekly (22 µg or 66 µg) or thrice-weekly (22 µg). Production of the pro-inflammatory cytokines IFN-γ and TNF-α was 2 to 3-fold stronger in patients receiving thrice-weekly dosing. While there was no apparent difference between the once-weekly doses of 22 µg and 66 µg, there was a significant difference between 66 µg given once-weekly and 22 µg given thrice-weekly, favoring the more frequent dosing schedule. These results are paralleled by the fact that no difference in clinical efficacy or on MRI measures was found between 30 µg and 60 µg doses of Avonex® given once-weekly (14). Taken together, these data suggest a ceiling effect for a single dose; moreover, they indicate that once-weekly dosing is likely to be less effective than more frequent dosing.
CLINICAL TRIALS

Clinical trials support the greater efficacy of higher doses and more frequent dosing of IFNβ. The pivotal BETaseron® trial (15,16) was the first to show a dose-dependent effect of IFNβ-1b on a number of clinical and MRI measures, with 8 mIU (250 μg) every other day being significantly more effective than 1.6 mIU (50 μg) every other day. Relapse measures (exacerbation rate, time to first and second relapse) and MRI measures were dose-sensitive. In general, differences between placebo and 8 mIU were statistically significant, whereas differences between 8 mIU and 1.6 mIU and placebo were not always significant.

Dose-response effects have also been demonstrated in the PRISMS and OWIMS trials. In the PRISMS (Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) trial (17), patients received 22 μg (low-dose) or 44 μg (high-dose) Rebif® or placebo thrice-weekly for 2 years. Both treatment groups showed a significant reduction in relapse rate (by 33% and 37% respectively), but for virtually all clinical variables examined, the high-dose group showed greater efficacy, although not to a statistically significant degree.

The higher dose did produce a significantly greater reduction in active MRI lesions than did the lower dose. In the OWIMS (Once Weekly Interferon for MS) trial, patients were given placebo or SQ IFNβ-1a at doses of 22 μg or 44 μg once-weekly for 1 year (18). Here, clinical results were less dramatic than in PRISMS, but still emphasize that efficacy is dose-dependent.

Double-blind extension data (19) from PRISMS provide clear evidence of dose-dependence for numerous clinical and MRI measures. At the end of the initial 2-year period, placebo patients were randomized to receive low or high-dose Rebif® thrice-weekly for an additional 2 years. The proportion of patients who had confirmed progression of disability was lowest for patients in the high-dose group for the entire 4 years and highest in patients who received placebo for the first 2 years and low-dose Rebif® for years 3 and 4. The effect was intermediate for patients in the low-dose group for the entire 4 years and patients randomized to the high-dose group after being on placebo for the first 2 years. This same pattern of efficacy was similar for clinical relapse and MRI (burden of disease and number of active lesions) measures. These results underscore the benefits of starting IFNβ treatment at the highest dose early in the disease.

In the MSCRG (Multiple Sclerosis Collaborative Research Group) trial, patients were randomized to either placebo or 30 μg IFNβ-1a (Avonex®) IM once-weekly (20). Reduction in relapse rate relative to placebo over one year of treatment was 9.6% (not statistically significant). A 32% reduction in relapse rate was claimed among patients followed at least 2 years, but this figure was derived from post hoc analysis of a subgroup. The overall reduction in relapse rate among all patients receiving Avonex® was 18% (P = 0.04) at 2 years. Other clinical outcome measures, such as proportion of relapse-free patients and time to first relapse, favored the Avonex®-treated group, but not in a statistically significant way.

The importance of dose frequency has not been properly addressed in Avonex® studies. Clanet et al. (14) have evaluated 30 μg versus 60 μg once-weekly and found no differences in progression over 3 years. A larger multicenter trial using Avonex® is in progress (21), but again, treatment groups are receiving 30 μg or 60 μg of Avonex® once-weekly. Based upon the numerous studies that emphasize the importance of dose frequency, a more telling study would have been one comparing 30 μg Avonex® at different dose frequencies. When data from the MSCRG, PRISMS and OWIMS studies are compared, an unequivocal dose-response is apparent regarding both clinical and MRI measures. Dose-response relationships are even stronger for MRI indicators than for clinical variables.

It is well accepted that IFNβs are more effective when used earlier in the disease process, and two studies have shown that IFNβ-1a treatment after an initial demyelinating event such as optic neuritis can delay progression to multiple sclerosis. The CHAMPS trial (22) showed a more substantial reduction in conversion to MS than did ETOMS (23); however, there are a number of differences between the two trials. Most importantly, ETOMS used a weekly dose of just 22 μg (which had no effect on relapse rate in established MS patients (18)), compared with 30 μg Avonex® in CHAMPS. Betaferon® is currently being investigated in patients presenting with a clinically isolated demyelinating syndrome (BENEFIT trial). This will represent the first early treatment trial using high-dose IFNβ.

HEAD-TO-HEAD TRIALS

In determining the effect of dose size and frequency, direct comparison of agents is most informative. Two head-to-head trials between IFNβ formulations have been carried out thus far, with results of the INCOMIN (BETaseron® versus Avonex®) (24) and EVIDENCE (Rebif® versus Avonex®) (25) trials recently revealed. In both trials, standard dosing, frequency and route of administration were implemented. The INCOMIN (Independent Comparison of Interferon) trial was an unsolicited multicenter randomized open-label study by Durelli and colleagues from Italy. At the end of a 1-year treatment period, IFNβ-1b (Betaferon®) proved significantly more effective than IFNβ-1a (Avonex®) in clinical and blinded MRI outcome measures (P < 0.05). Two-year results, initially presented at the September, 2001 ECTRIMS meeting in Dublin, Ireland, with full results presented at the Italian Neurological Society meeting in October, 2001, indicate that differences favoring Betaferon® became even more notable during the second year. The primary clinical outcome measure, number of relapse-free patients, was greater in Betaferon®-treated patients: 51% versus 36% at 2 years (Betaferon® versus Avonex®, P < 0.036). In addition, fewer patients in the Betaferon® group had an EDSS increase of at least 1.0
point at 6 months that was sustained at 2 years: 14% versus 30% (Betaferon® versus Avonex®, P < 0.005). MRI measures also favor Betaferon®. Of the patients receiving Betaferon® for 24 months, 55% were free of new T2 lesions compared with only 26% of those on Avonex® (P = 0.0003).

The EVIDENCE study (25), a randomized, open-label, assessor-blinded study designed to compare IFNβ-1a (Rebif®) 44 μg SQ thrice-weekly to IFNβ-1a (Avonex®) 30 μg IM once-weekly, has shown a statistically significant reduction in relapses and MRI burden of disease at 24 weeks, favoring Rebif®. Rebif® proved significantly more effective than Avonex® for all clinical and MRI outcome measures. The primary outcome measure, the proportion of patients remaining relapse-free at 24 weeks, was 74.9% in the Rebif® group and 63.8% in the Avonex® group (P = 0.005). The principal secondary outcome measure was combined unique active-lesion number based on monthly scans; the number of new MRI lesions per patient per scan was 0.8 in the Rebif® group and 1.2 in the Avonex® group (P < 0.0001). Although mild adverse events such as injection-site reactions were more common in the Rebif® group, there was no difference in terms of serious adverse events, which were infrequent in both groups. Systemic side effects due to IFNβ were slightly higher for Avonex®. The data for 48-week outcomes in the EVIDENCE trial are being analyzed.

Thus, there is substantial evidence indicating dose-dependency for both IFNβ-1b and IFNβ-1a treatment effects on biologic response, immunologic mechanisms, clinical parameters that relate to relapses and overall disability, and MRI measures of disease activity. While there may be a ceiling effect with once-weekly dosing, this frequency of injection appears to be inadequate. Certainly, the convenience of once-weekly dosing needs to be weighed against the overwhelming evidence that supports greater efficacy at higher, alternate day dosing. In light of data from CHAMPS and ETOMS, and with increasing evidence that irreversible axonal injury occurs early in the course of MS, early treatment with disease-modifying therapy is recommended. Results of the PRISMS 4-year data indicate that early introduction of high-dose IFNβ provides benefit over low-dose therapy. For IFNβs, more is better.

REFERENCES

Optic Disc Topography in Pseudopapilledema: A Comparison to Pseudotumor Cerebri

Gary L. Trick, PhD, Sonali S. Bhatt, BS, David Dahl, MS, and Barry Skarf, PhD, MD

Objectives: To determine if confocal scanning laser (CSL) tomography can quantify optic disc topography in patients with pseudopapilledema (PP) and to contrast the regional topography of the optic disc in PP and pseudotumor cerebri (PTC).

Materials and Methods: Three-dimensional optic disc images from 10 PP patients and 17 PTC patients were obtained using the Heidelberg Retinal Tomograph (HRT). Two conventional HRT parameters, volume above the reference plane and volume above the surface, were used to quantify global disc elevation. In addition, local topography was determined at 100 (μm) intervals along eight meridians at 100 to 1700 (μm) from the disc center. The global and local measures of disc topography in the two groups were compared statistically.

Results: Significant between group differences were detected for both global measures. Regional analysis revealed vertical symmetry and horizontal asymmetry in PP and PTC as well as significant between group differences in peripapillary height. Conclusions: CSL tomography can quantify disc elevation in both PP and PTC and may be useful for differentiating disc morphology in PP and PTC. The volume of the disc above the retinal surface is greater in PTC than in PP. However, most of the difference in elevation between the two groups occurs over the disc rim and peripapillary retina.

Key Words: Confocal scanning laser tomography—Optic disc—Pseudopapilledema—Pseudotumor cerebri.

Papilledema is a diagnosis that describes true swelling (edema) of the optic disc resulting from elevated intracranial pressure (ICP). Pseudopapilledema refers to an optic nerve anomaly in which there is elevation of the optic disc surface and blurring of its margins that can resemble papilledema or the disc edema associated with other optic neuropathies. Unlike true edema of the optic disc, pseudopapilledema (PP) is considered benign and is frequently related to the presence of optic disc drusen, which are calcific bodies within the optic nerve head. Papilledema, on the other hand, can be caused by a space-occupying intracranial lesion such as a tumor or hemorrhage. Frequently, however, papilledema is associated with an idiopathic elevation of ICP, a condition known as pseudotumor cerebri or as benign intracranial hypertension. Since the optic disc can appear outwardly similar in papilledema and pseudopapilledema, careful evaluation of the disc morphology is often critical in diagnosing these conditions. Clinically, differentiating papilledema from PP can be a challenge for most physicians, neurologists, neurosurgeons, optometrists and for many ophthalmologists. When the diagnosis is uncertain, patients are referred for neuroimaging studies to rule intracranial pathology. More reliable and simple methods to distinguish PP from true disc swelling would help eliminate much uncertainty, unnecessary hardship, expense, and worry.

Confocal scanning laser (CSL) tomography provides a direct, noninvasive, quantitative evaluation of optic disc morphology. The accuracy, reliability, and reproducibility of this technique when used to measure optic disc excavation in glaucomatous optic neuropathy have been demonstrated (1-3). Recently, CSL tomography has also been shown to be useful as a means of measuring and monitoring the optic disc elevation due to papilledema in patients with pseudotumor cerebri (PTC) (4-6). CSL tomography also has been demonstrated to have a high sensitivity for detecting small changes in disc volume in PTC patients (5). Consequently, it has been suggested that CSL tomography might be useful for the follow-up of these patients (6). We are unaware of any published studies in which CSL tomography was used to systematically evaluate optic disc topography in PP. Therefore, this study was designed to determine if CSL tomography could be used to accurately quantify optic
posterior to the mean height of the retinal surface, that is reference plane is specified by its absolute or relative z coordinate (height). In the version 2.01 software the reference plane is automatically defined at a location 50 μm from the center of the optic disc. The volume above the reference plane is defined as the volume within the contour line; all connecting lines from the center point to a boundary point are straight lines. For purposes of this study the contour line that was drawn at 1800 μm from the center of the optic disc.

To further refine the analysis and evaluate the regional topography of the papilla and peripapillary retina, the HRT data were transformed as follows. With 0° defined as temporal, eight meridians were selected for analysis. As illustrated in Figure 1, the eight meridians ranged from 0° to 315° in 45° increments. Mean retinal elevation was then calculated for each of the 17 positions along each meridian, determined in 100 μm steps from 100 to 1700 μm from the center of the optic disc. In this procedure the center of the optic disc is defined as the center of gravity of all points along the contour line and automatically determined. At each of these positions the retinal surface height was calculated as the mean surface height along an arc extending ± 22.5° from each meridian on the circumference of a ring one pixel wide and having the same radius as the location. The mean retinal surface height for each location is then expressed relative to the mean surface height determined for a ± 5° arc centered at a radius of 1700 μm from the center of the optic disc along the 0° meridian (i.e., normalized relative to this reference value in a flat retina).

FIG. 1. Sections of the optic disc selected for analysis consist of eight meridians ranging from 0° to 315° in 45° increments. The temporal meridian was defined at 0°. Mean retinal elevation was calculated for 17 positions along each meridian from 100 to 1700 μm in 100 μm increments. At each of these positions the retinal surface height was calculated as the mean surface height along an arc extending ± 22.5° from each meridian on the circumference of a ring one pixel wide and having the same radius as the location. This value is expressed normalized relative to a reference value in a flat retina.


**METHODS**

**Procedure**

The Heidelberg Retinal Tomograph (HRT, Heidelberg Engineering, Heidelberg, Germany) was used to image the optic disc. The HRT is a confocal microscope that uses a 650-nm diode laser to scan the retinal surface in three dimensions. To generate three-dimensional topographic images, the HRT acquires a series of transverse optical sections taken at 32 consecutive equally spaced focal planes over a scan depth that ranges from .5 to 4.0 mm. Each image is generated from a 256 by 256 pixel matrix (65,536 pixels) in which each pixel represents retinal surface height at a specific location. The section images are automatically aligned for horizontal and vertical shifts due to any fixation instability during acquisition of the image. By combining the images in each series, the software generates a topographic map (also containing 256 by 256 pixels) in which each pixel has a value describing surface elevation at that point. These images are rapidly obtained. (Total acquisition time is approximately 1.6 seconds for the 32 images). The elevation measures are expressed relative to a reference plane that, in this study, was chosen to be the focal plane of the eye (see later discussion).

A 15° by 15° image, centered relative to the optic disc, was chosen for all images obtained in this study. Images were acquired using the standard HRT protocol (version 2.01) in which the elevation of the retinal surface is calculated relative to a reference plane placed 50 μm posterior to the mean retinal elevation along an arc concentric with the optic disc margin in the temporal segment of the optic disc (350° to 356°). Three topographic images were obtained through the undilated pupil for each eye and every image was corrected for tilt using a (pre-programmed) conventional HRT analysis. The mean retinal surface height was calculated as the mean surface height along an arc extending ± 22.5° from each meridian centered at a radius of 1700 μm from the center of the optic disc. The mean retinal surface height for each location is then expressed relative to the mean surface height determined for a ± 5° arc centered at a radius of 1700 μm from the center of the optic disc along the 0° meridian (i.e., normalized relative to this reference value in a flat retina).

**Analysis**

The (pre-programmed) conventional HRT analysis measures two parameters that have been shown to be associated with the degree of optic disc swelling. These parameters are the volume above reference plane and the volume above surface. The volume above the reference plane is defined as the volume within the contour line that is above the reference plane. The HRT software permits the definition of reference planes parallel to the (x, y) plane of the coordinate system. A reference plane is specified by its absolute or relative z coordinate (height). In the version 2.01 software the reference plane is automatically defined at a location 50 μm posterior to the mean height of the retinal surface, that is at z = -50 μm in the relative coordinate system. Therefore, volume above the reference plane is a measure of the tissue volume inside the contour line that is anterior to this reference plane.

The volume above the surface is the volume within the contour line that is above the curved surface. The curved surface lies on the contour line at every boundary point, following the height variation of the retinal surface along the contour line. The height in its center is specified by the mean height of the retinal surface along the disc contour line; all connecting lines from the center point to a boundary point are straight lines. For purposes of this study the contour line that was drawn at 1800 μm from the center of the optic disc.

The (pre-programmed) conventional HRT analysis measures two parameters that have been shown to be associated with the degree of optic disc swelling. These parameters are the volume above reference plane and the volume above surface. The volume above the reference plane is defined as the volume within the contour line that is above the reference plane. The HRT software permits the definition of reference planes parallel to the (x, y) plane of the coordinate system. A reference plane is specified by its absolute or relative z coordinate (height). In the version 2.01 software the reference plane is automatically defined at a location 50 μm posterior to the mean height of the retinal surface, that is at z = -50 μm in the relative coordinate system. Therefore, volume above the reference plane is a measure of the tissue volume inside the contour line that is anterior to this reference plane.

FIG. 1. Sections of the optic disc selected for analysis consist of eight meridians ranging from 0° to 315° in 45° increments. The temporal meridian was defined at 0°. Mean retinal elevation was calculated for 17 positions along each meridian from 100 to 1700 μm in 100 μm increments. At each of these positions the retinal surface height was calculated as the mean surface height along an arc extending ± 22.5° from each meridian on the circumference of a ring one pixel wide and having the same radius as the location. This value is expressed normalized relative to a reference value in a flat retina.
Subjects

All study procedures were conducted in accordance with the tenets of the Declaration of Helsinki. Optic nerve head images were collected from 10 patients with clinically diagnosed pseudopapilledema (PP) ranging from 14 to 57 years of age (mean = 32.2 ± 14.0 years). The results for the PP patients were compared with data from 17 patients with clinically diagnosed pseudotumor cerebri who were 10 to 39 years of age (mean = 31.5 ± 7.0 years). The diagnosis of PTC was based on the observation of clinical papilledema on funduscopic examination in the presence of elevated CSF pressure and a negative CT scan of the head. Patients with pseudopapilledema were selected from among those referred with a diagnosis of possible papilledema and from among patients who were diagnosed with pseudopapilledema on routine examination, only when they met the following criteria: 1) abnormal elevation of the optic disc; 2) indistinct disc margin; 3) retinal vessels of normal caliber; 4) spontaneous venous pulsations present; 5) no obscuration of any vessels crossing the disc margin; 6) no retinal or disc hemorrhage or exudate; 7) appearance unchanged on six month follow-up exam.

Individuals with more than 6.0 diopters of either myopia or hyperopia or more than 1.0 diopter of astigmatic error were excluded. Individuals with a prior history of ophthalmic disease or any systemic disease with ocular manifestations were excluded.

Statistical Analysis

For comparison with previously published reports (5–7), the mean “volume above the reference” and the mean “volume above the surface” were determined and for each of these parameters the difference between groups was assessed using a Student t test.

For the regional analysis statistical comparisons were based upon the normalized retinal elevations determined for each of the 17 positions along each meridian. A descriptive analysis of the variation in retinal elevation along each meridian was generated based upon the mean elevation at each distance from the center of the optic disc in both patient groups. The surface height values for each of the 17 locations along the eight meridians in the PP group were compared with those of the PTC group utilizing Student t test.

Results

The “volume above the reference” was determined for all patients in each group (Fig. 2). The mean “volume above the reference” was lower for the PP patients (2.821 ± 1.215 mm³) than for the PTC patients (4.556 ± 2.379 mm³). The between-group difference was statistically significant: P = 0.0038. For each participant the “volume above the surface” was also determined (Fig. 3). The mean “volume above the surface” was less for the PP patients (1.730 ± 1.062 mm³) than for the PTC patients (2.793 ± 1.498 mm³) and this difference also was statistically significant (P = 0.0075).

In order to identify the local factors contributing to these global differences between groups, the mean surface height as a function of distance along each meridian was calculated for all eight meridians. In the PP patients, maximal surface height was greatest in the superonasal region where it exceeded 530 µm. Maximum surface height also exceeded 500 µm in the nasal (513 µm) and inferonasal (512 µm) meridians (Fig. 4). Maximum surface height was least in the temporal (154 µm) and inferotemporal (280 µm) meridians (Fig. 4). Other meridians were intermediate. Overall surface topography in the PP group was symmetrical along the vertical axis and asymmetric along the horizontal axis. Surface height in the nasal aspect peaked at 400 µm from the center of the optic disc while in the temporal aspect surface height peaked at 600 µm from the center of the optic disc. Along the vertical axis, surface height peaked at 600 µm from the center of the disk while inferiorly surface height peaked at 700 µm from the center. Along the oblique axes the symmetry was intermediate between the vertical and horizontal axes with peak surface height between 500 and 700 µm from the center of the optic disc.

A similar trend was observed in the PTC group with retinal surface height greatest in the superonasal and
OPTIC DISC IMAGING IN PSEUDOPAPILLEDEMA

Distance from Center of Optic Disc

FIG. 4. Relative retinal elevation for each of the 17 points along eight meridians are shown for PP patients. Elevation and distance from the center of the disc are given in μm. Meridians are defined as follows: IN-ST, Infranosal to superotemporal, an oblique axis; I-S Inferior to superior, the vertical axis; IT-SN, Inferotemporal to superonasal, an oblique axis T-N, Temporal to nasal, the horizontal axis.

least in the temporal aspects of the disc (Fig. 5). Surface height was asymmetric along the horizontal axis with little elevation temporally compared with nasally. Surface height reached a maximum at 500 μm from the center of the disc nasally and at 700 μm temporally. Along the vertical axis, elevation was essentially symmetric, reaching a peak at 800 μm from the center of the disc both superiorly and inferiorly. As was the case for the PP patients symmetry along the oblique axes was intermediate between the vertical and horizontal axes (Fig. 5).

As suggested by the global analysis, mean surface height was generally greater in the PTC patients than in the PP patients (Fig. 6). For all eight meridians, the difference between the two groups was essentially zero in the center of the papilla and increased to reach a maximum at 900 to 1200 μm from the center of the optic disc. The difference in surface height decreased more peripherally. For each of the meridians, the surface height differences were generally symmetrical although there was a somewhat greater asymmetry in the vertical than in the horizontal axis. Along the horizontal axis the difference in retinal surface height between the two groups is symmetrical with the difference in surface height reaching 240 μm nasally and 237 μm temporally. In both cases, the maximum between group differences was found at 900 μm from the center of the disc. For the superior meridian, the between group difference in surface height difference peaked (270 μm) at 1200 μm from the center of the disc while inferiorly the greatest difference (222 μm) was detected at 1100 μm from the center of the disc (Fig. 7).

To describe the difference in surface height between the two groups more precisely, Student t tests were used to compare measurements for each of the locations along all eight meridians. No statistically significant differences were observed within a circle of radius 500 μm from the center of the papilla. The most significant between group differences were detected in the peripapillary retina: 1) Superiorly at 1300 μm (P = 0.000916) and 1400 μm (P = 0.000721) 2) Superonasally at 1300 μm (P = 0.000906) and 1400 μm (P = 0.000833) and 3) Intertemporally at 1100 μm (P = 0.00094).

DISCUSSION

In pseudopapilledema there is an elevation of the optic disc that appears similar to the papilledema associated with pseudotumor cerebri. However, the optic disc elevation in pseudopapilledema is usually secondary to an underlying benign process such as optic disc drusen, whereas the papilledema in PTC is a direct result of elevated intracranial pressure. Given the distinct mechanisms mediating the optic disc changes in these two conditions, we speculated that careful quantitative evaluation of the optic disc morphology could reveal differences in disc topography reflecting the diverse pathophysiology. Reliable topographic differences between the two conditions could also be useful for differential diagnosis.

We found that SLO tomography could be used to quantify optic disc topography in both PP and PTC. Several previous reports have documented the utility of SLO tomography in PTC but we believe this is the first report on the use of SLO tomography to quantify optic disc topography in PP. We observed a significant anterior displacement of the papillary and peripapillary surfaces in PTC patients. The magnitude and position of this anterior displacement was similar to what has been reported previously. In particular, surface topography in the PTC group was symmetrical along the vertical axis and asymmetric along the horizontal axis. In the PTC group surface height peaked at between 500 and 800 μm.
FIG. 7. The optic disc is represented by regions, the concentric circles indicate distance from the center of the disc in microns. This is a composite showing the between group differences that were statistically significant and their values. The most statistically significant differences between PP and PTC are located at the supranasal and infratemporal regions.

from the center of the optic disc (depending upon the meridian) and was greatest in the superonasal, nasal, and superior regions and least in the temporal region.

In the PP patients the gross optic disc morphology appeared similar to the PTC patients. Surface height peaked at between 400 and 700 μm from the center of the optic disc depending upon the meridian and was greatest in the superonasal, nasal, and inferonasal regions and least in the temporal region.

Despite these similarities, quantitative analysis revealed distinct differences between the two groups. Significant differences in “volume above the reference” and “volume above the surface” were detected indicating that surface height was generally lower for PP patients than for PTC patients. However, local analysis revealed that the surface height differences were not uniform. Comparison of retinal elevation values for each location along all meridians demonstrated that PP and PTC have differences that are statistically significant particularly at the superonasal, temporal, and inferonasal aspects of the disc. Furthermore, in the central 500 μm of the papilla no statistically significant differences between PP and PTC were detected, while near the neuroretinal rim and in the peripapillary retina PP patients exhibited significantly lower surface height than PTC patients in all meridians. This finding indicates that the disc swelling of papilledema extends well beyond the disc margin elevating peripapillary retina, as well as the optic disc. In contrast, the elevation due to PP is more closely confined to the papilla itself. Thus, the pathophysiologies underlying the two diseases appear distinct, producing a larger area as well as a greater magnitude of elevation in the PTC patients.

This study also demonstrates that measures of regional optic disc topography localize similarities and differences between PP and PTC that are not evident in the global measures of disc volume. This finding implies that quantitative regional topography may be more sensitive to subtle differences optic disc morphology than the conventional HRT analysis. However, further investigation is needed to determine if the HRT can be used to monitor the progression or remission of regional differences.

In conclusion, this study demonstrated that the HRT could quantify optic disc topography in pseudopapilledema as well as in pseudotumor cerebri. Therefore, the HRT can be used as a reliable method of measuring the optic disc elevation as well as excavation. Although the standard HRT procedures require delineation of a contour line at the margin of the optic disk, the technique we present here allows a less subjective measure of the degree of elevation in the optic disc. The surface elevation measurements at various selected meridians allow for an accurate composite picture of the regional topography in both conditions. Recognition of regional differences in the degree of elevation may be beneficial to the clinician detecting an apparently swollen disc but unsure of whether it is the result of a benign process (such as pseudopapilledema) or an indication of elevated intracranial pressure.

REFERENCES

Polarimetric Nerve Fiber Analysis in Patients with Visible Optic Nerve Head Drusen

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Objective: To evaluate the effect of visible optic nerve head drusen (ONHD) on retinal nerve fiber layer (RNFL) thickness retardation by using scanning laser polarimetry.

Methods: Twenty-three eyes of 13 patients with visible ONHD and 26 eyes of 13 age- and sex-matched control subjects were involved in the study. Ophthalmologic examination, scanning laser polarimetry with nerve fiber analyser (NFA) type II GDX, automated Humphrey visual field testing, and red-free fundus photography were performed. Eyes with ONHD were classified from grade 0 to III according to the amount of visible drusen. Thus, grade 0 discs had no clinically visible ONHD and grade III discs represented the presence of dense drusen.

Results: Measurements with NFA of RNFL thickness retardation showed significant decrease in eyes with visible ONHD compared with control eyes (P < 0.05). Although no significant difference was found between grade I and grade II discs regarding NFA measurements, grade III discs had significantly lower values, indicating the greater amount of RNFL loss with higher grade ONHD. Documentation of increased percentage of visual field defects with higher grade drusen was also in accordance with this finding.

Conclusions: NFA can quantitatively detect the decrease in retardation of RNFL thickness in eyes with visible ONHD and can be used as an indicator of nerve fiber layer loss in these cases.

Key Words: Optic nerve head drusen—Retinal nerve fiber layer—Nerve fiber analyser—Visual field.

Optic nerve head drusen (ONHD) were first described clinically by Liebreich in 1868 (1). These hyaline structures appear as globular bodies protruding from optic disc and blur the disc margins. They are mostly bilateral and often familial. Lorentzen reported an incidence of 3.4 per 1000 individuals (2). ONHD are mostly seen in small discs (3). A small scleral canal is thought to cause stasis of axoplasmic flow and result in death of ganglion cell axons and formation of ONHD. This build-up of drusen, in turn, damages progressively more axons. The result is retinal nerve fiber layer (RNFL) atrophy and associated visual field defects. These visual field defects are similar to those of glaucoma or other optic neuropathies (2). Since ONHD distort the optic disc shape, it is also quite difficult to interpret the cupping.

The RNFL can be evaluated with several different techniques, such as red-free ophthalmoscopy, photography, optical coherence tomography (OCT), scanning laser tomography, scanning laser microperimetry, laser biomicroscopy, and scanning laser polarimetry (4-6). RNFL defects associated with ONHD were previously documented by RNFL photography and, more recently, by OCT (5,6). In this study, the RNFL in eyes with visible ONHD is evaluated by scanning laser polarimetry, a diagnostic technique that measures the thickness of peripapillary RNFL in vivo quantitatively (7). This method does not require a reference plane and provides rapid and objective data.

PATIENTS AND METHODS

Between November 1998 and December 1999, 26 eyes of 13 patients with visible ONHD were examined at our Ophthalmology Department. Ophthalmologic evaluation included visual acuity testing, intraocular pressure measurement (Goldmann tonometry), slit-lamp examination, indirect slit-lamp biomicroscopy with +90 D lens, color and red-free photography using a digital fundus camera (FF 450 IR; Zeiss, Oberkochen, Germany), and automated visual field examination with Humphrey central threshold program (30-2 or 24-2) (Humphrey Allergan Instruments, San Leandro, CA, USA). Scanning laser polarimetry and visual field testing were performed...
The inclusion criteria were the presence of ONHD visible by indirect slit-lamp biomicroscopy in one or both eyes and the absence of any other known ocular pathologic lesion affecting the RNFL (e.g., glaucoma and other optic neuropathies, previous retinal surgery or retinal laser treatment). Eyes with ONHD were graded from 0 to III according to the ophthalmoscopic appearance of drusen (6). Grade 0 discs had no clinically visible ONHD. Grade I discs had a few scattered drusen, and grade II discs had more numerous ONHD. Grade III discs were noted to have dense drusen with obscuration of the optic cup (Fig. 1).

A nerve fiber analyser (NFA II GDX version 1.0.08; Laser Diagnostic Technologies Inc, San Diego, CA, USA) was used to measure the thickness of the RNFL. This noninvasive technique is described in detail elsewhere (8-11). Briefly, NFA consists of a laser source, a polarizer, a scanning unit, a polarization modulator, a compensator, and a polarization detector. NFA projects 780 nm polarized laser light on the retina. The parallel microtubules within the retinal ganglion cell axons behave as a birefringent medium and change the polarization state of laser light. The phase shift of polarization is called "retardation" and is presumed to be linearly correlated to RNFL thickness. The compensator corrects for the effect of lens and corneal birefringence on the RNFL retardation measurement.

The RNFL thickness is calculated automatically in each of 256x256 individual retinal positions. To eliminate any operator-related bias, measurements were performed by the same trained examiner (BB). To avoid the effect of corneal birefringence on the measurements, macular scans were performed. None of the patients or the control subjects displayed axes or amplitudes not corrected by the commercial device. The field size was set to 15x15 degrees and pupils were undilated. Three good-quality images were obtained and results were averaged (Fig. 2). The measuring ellipse was positioned along a line at 1.5 disc diameters concentric with the disc margin. Two parameters, namely ellipse average (EA) and total polar integral (TPI), calculated by NFA were used for comparison between the patients with visible ONHD and control subjects (8). Briefly, EA (in microns) is the average thickness of the RNFL beneath the ellipse surrounding the optic disc. The integral under the retardation curve (polarimetric data analysis), which represents the cross-sectional area of the RNFL along the measuring ellipse, is also calculated (TPI, in mm²).

Twenty-six eyes of 13 age- and sex-matched normal subjects, taken as controls, also underwent ophthalmologic examination, including scanning laser polarimetry with NFA and visual field testing with Humphrey 30-2 threshold program. These subjects were free of ocular disease with 20/20 vision in each subject, intraocular pressures less than 21 mm Hg, and normal-appearing optic discs.

Statistical analysis was performed using the Mann-Whitney U test and an independent, two-tailed Student t-test. A P value of less than 0.05 was considered statistically significant.

RESULTS

There were six male and seven female subjects in the visible ONHD group with an average age of 29.6 (SD, 19.6) years (range, 12–68). Of the 13 age-matched control subjects, 6 were male and 7 were female with an average age of 29.6 (SD, 18.9) (range, 12–65). Except...
for three unilateral cases, all other patients had bilateral visible ONHD. Among the three unilateral cases, ONHDs were visible in one OD and two OSs. Thus, a total of 23 eyes with visible ONHD were involved in the study. There were 7 grade I, 10 grade II, and 6 grade III discs. In 7 of 10 bilateral cases, ONHD grades were the same. Visual acuities ranged from 20/20 to 20/30 in eyes with visible drusen. The results of two parameters (EA, TPI) (mean [SD]) of eyes with visible ONHD and control eyes are given in Table 1 and Figures 3 and 4. Comparisons of RNFL thickness measurements were made between the eyes with visible drusen (all grades as a single group) and control eyes, between each of the three grades and controls, and finally between each grade of ONHD.

Both parameters (EA, TPI) indicated a significant decrease in retardation of RNFL thickness in eyes with visible drusen (67.2 μm and 0.576 mm², respectively) compared with those of control eyes (81.03 μm and 0.697 mm², respectively; \( P = 0.0001 \) for both parameters, two-tailed Student t-test) (Figs. 3 and 4).

When each grade of ONHD was compared with control eyes, only a subset of age- and sex-matched control subjects rather than the whole control group was used for each comparison. Grade I discs differed from the control discs significantly in both EA and TPI with \( P = 0.043 \) and \( P = 0.003 \), respectively (Mann-Whitney U test). When grade II discs were compared with the control discs, the difference was significant with regard to EA and TPI (\( P = 0.041 \) and \( P = 0.048 \), respectively, Mann-Whitney U test). The most significant difference was between grade III discs and control discs, however (\( P = 0.0001 \) for both parameters, Mann-Whitney U test) (Table 1).

When ONHD grades were compared with each other, no statistically significant difference was found between grade I and II discs (\( P > 0.05 \), Mann-Whitney U test). Both parameters showed a significant decrease in retardation in grade III discs compared with grade I discs (EA, \( P = 0.005 \); TPI, \( P = 0.048 \); Mann-Whitney U test). When grade II discs were compared with grade III discs, EA measurement showed a significant difference, indicating that the RNFL was thinner in grade III ONHD (\( P = 0.022 \), Mann-Whitney U test) (Table 1).

### Table 1. Retardation due to retinal nerve fiber layer thickness (mean [SD]) and percentage of visual field defects of eyes with optic nerve head drusen (ONHD) and of control eyes

<table>
<thead>
<tr>
<th></th>
<th>Eyes (n)</th>
<th>EA (μm)</th>
<th>TPI (mm²)</th>
<th>% with VFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>26</td>
<td>81.03 (12.1)</td>
<td>0.697 (0.10)</td>
<td>0</td>
</tr>
<tr>
<td>ONHD (Total)</td>
<td>23</td>
<td>67.2 (10.08)</td>
<td>0.576 (0.07)</td>
<td>60.8</td>
</tr>
<tr>
<td>Grade I</td>
<td>7</td>
<td>70.0 (5.4)</td>
<td>0.563 (0.05)</td>
<td>42.8</td>
</tr>
<tr>
<td>Grade II</td>
<td>10</td>
<td>70.0 (1.1)</td>
<td>0.617 (0.09)</td>
<td>50</td>
</tr>
<tr>
<td>Grade III</td>
<td>6</td>
<td>57.8 (6.7)</td>
<td>0.523 (0.03)</td>
<td>100</td>
</tr>
</tbody>
</table>

EA, ellipse average; TPI, total polar integral; VFD, visual field defects.

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**Fig. 2.** Scanning laser polarimetric image of the eye in Figure 1. A: Graph showing the RNFL thickness in temporal, superior, nasal, inferior, and temporal quadrants, compared with the normative database. Measurements of the patient are almost at the same level in temporal and nasal quadrants but below the lower limit of normative database in some parts of inferior and superior quadrants. Note the attenuation of the typical double hump of RNFL indicating nerve fiber layer thinning. B: Fundus image of patient. C: Thickness map; showing thicker RNFL (dark) in the superior and inferior quadrants, and thinner RNFL (light) in the nasal and temporal area; however, in this patient there is an overall decrease in RNFL.
Visual field defects were present in 42.8% of patients with grade I, 50% of patients with grade II, and 100% of patients with grade III ONHD (Table 1). Most common field defects are found to be blind spot enlargement and arcuate defects followed by inferonasal defects and generalized constriction (Fig. 1).

**DISCUSSION**

Alteration in axonal transport seems to be the basic pathogenic mechanism for the formation of ONHD (3). A small scleral canal is thought to cause stasis of axoplasmic transport at the optic nerve head and result in accumulation of hyaline material (12). This accumulation of hyaline material further impedes the axoplasmic flow and causes death of more axons. Thus, ONHD is a progressive disease in which resulting RNFL atrophy is manifested as visual field defects, reported in 71% of eyes with visible drusen (13). Generally, these defects show a nerve fiber bundle pattern similar to that of glaucoma; however, visual field defects do not necessarily match the position of drusen in the optic disc (14). Two major theories proposed for the development of visual field defects can be summarized as direct compression of RNFL by drusen or vascular events caused by drusen.

Several methods have been used for the evaluation of RNFL in eyes with ONHD. Mustonen and Nieminen performed photography to document atrophy of the peripapillary RNFL (5). However, interpretation of RNFL photography is subjective and often difficult. Recently, OCT was shown to document the nerve fiber layer thinning due to ONHD (6). OCT is a noninvasive and noncontact technique that incorporates near infrared, coherent light passing through Michelson interferometer (15). It gives high-resolution, cross-sectional imaging of the retina. With OCT, superior and inferior RNFL measurements were found to be significantly thinner in eyes with visible drusen compared with in control eyes. Higher grade ONHD had more visual field defects in accordance with thinner RNFL measurements by OCT (6). Our data, similarly, have disclosed that higher grade ONHD was associated with visual field defects and decreased retardation values.

In this study, we used NFA to evaluate RNFL thickness in eyes with visible ONHD. NFA is a computerized scanning laser polarimetry device that can objectively and quantitatively measure the RNFL thickness in terms of retardation in vivo. In patients with glaucoma and ocular hypertension, a reduction of RNFL thickness retardation was documented by NFA (10,11). It works with undilated pupils, and a complete scan of 65,536 points takes only 0.7 seconds. Although placing the measuring ellipse at the disc margin for grade III discs was relatively difficult, the experienced operator could establish disc border by using the segments of disc margin uninvolved by ONHD. In this study, NFA parameters dealing with the whole circumference of optic disc (EA, TPI) were used rather than sectoral (superior, inferior, temporal, nasal) thickness measurements, since it was previously documented that visual field defects do not necessarily match the localization of drusen in the optic disc. We found that there was a significant reduction in retardation of RNFL thickness compared with controls. Presence of visual field defects was in accordance with this finding. Grade III discs showed the most significant decrease in retardation, and all of the patients with grade III discs had visual field defects. On the other hand, grade I and II discs had similar measurements with a similar percentage of visual defects.

In conclusion, NFA can quantitatively detect the RNFL thickness retardation in eyes with visible ONHD. Eyes with visible ONHD had significantly lower RNFL thickness retardation values compared with normal eyes. With increasing grades of ONHD, the nerve fiber layer loss was found to be more prominent. NFA appears to be a sensitive indicator of RNFL loss. Further longitudinal studies are needed to assess the efficacy of NFA to document progressive RNFL changes in patients with visible ONHD.
REFERENCES

Vertical Saccades in Superior Oblique Palsy and Brown’s Syndrome

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Objective: To compare saccadic dynamics in superior oblique palsy and Brown’s syndrome.

Methods: Vertical saccades in adduction and in abduction were studied in two subjects with superior oblique palsy and one with Brown’s syndrome. Using large numbers of centrifugal saccades over a wide range of amplitudes, we measured peak velocity, duration, and the peak velocity/mean velocity ratio (PV/MV) as a function of saccadic amplitude. We compared vertical saccades in 30 degrees of abduction with those in 30 degrees of adduction.

Results: Superior oblique palsy caused a 15–18% reduction in peak velocities in adduction compared with abduction. Saccadic duration was also increased in adduction, with the result that there was no net change in the PV/MV ratio. In the patient with Brown’s syndrome, velocities and durations of upward saccades were similar in abduction and adduction, but the PV/MV ratio was significantly elevated in adduction. We also observed an unusual high-speed lateral ‘snap’ of about 5 degrees that frequently interrupted vertical saccades in the midline but not elsewhere.

Conclusion: Both paresis and restriction of the superior oblique alter vertical saccades. The effects of restriction on saccadic dynamics are distinct from the effects of paresis.

Key Words: Superior oblique—Brown’s syndrome—Saccades—Restriction.

The contributions of the oblique muscles of the eye to rotation of the globe are complex. Though their primary actions are cyclotorsion of the globe, (excyclotorsion in the case of the inferior oblique and incyclotorsion for the superior oblique) (1), they also have secondary vertical actions, elevation for the inferior oblique and depression for the superior oblique. The magnitudes of their primary and secondary actions are dependent upon horizontal direction of gaze: theoretically, their torsional effect should be maximal at 60 degrees of abduction, and their vertical contribution maximal when the eye is adducted 30 degrees (1). This variation can be understood from considering the effective line of pull of these muscles on the eye, which is towards the anteromedial corner of the orbit, where the origin of the inferior oblique and the trochlea are located.

The effects of superior oblique paresis on static eye position are predictable from the three actions of the muscle (2): excyclotorsion, hypertropia of the affected eye, which is worse in adduction and ipsilateral head tilt, and a small esotropia often worse in depression (V-pattern). Conversely, superior oblique restriction, also known as Brown’s syndrome, limits the ability of the eye to elevate in adduction, sometimes with hypotropia of the affected eye in primary position.

The impact of oblique muscle dysfunction on ocular motor dynamics is less well known. In particular, their impact upon vertical saccades is controversial. Early experimental studies with novocaine injections found a small reduction in saccadic velocities (3). An electro-oculographic study appeared to confirm this by finding a mean 25% reduction of downward saccades in adduction in 8 patients with superior oblique palsy (4). However, another electro-oculographic study failed to find a difference in 18 patients (5). Citing potential difficulties in measuring vertical eye movements with electro-oculography, a more detailed study used the magnetic search coil technique to study 10 patients with superior oblique palsy and found no difference between the patient and the control groups (6). Conflicting findings were also found in a few patients studied before and after superior oblique tenotomy (4,5).

In interpreting these findings, it is important to note that the two negative studies reported primarily group means and group statistics. Given that the dominant depressor in all positions of gaze is the inferior rectus, and
that the theoretical maximal contribution of the superior oblique to depression is 18% (7), the effect on downward saccadic velocity of even complete paresis of this muscle is bound to be small. A group study is likely to include patients with palsies of varying severity, and with the wide variability in normal saccadic metrics, it is hardly surprising that small group analyses should fail to find a difference. While these negative studies (5,6) suggest that vertical saccadic velocity is not a sensitive test for superior oblique palsy, a group analysis cannot answer the more specific question of whether the superior oblique makes any contribution to vertical saccades. To address this, only patients with severe superior oblique palsy should be studied individually. In support, we note that both negative studies mentioned a few individuals whose downward velocities were impaired.

We performed detailed saccadic evaluation on two subjects with superior oblique palsy to address the question of the contribution of this muscle to vertical saccades. In addition, we studied one subject with a congenital Brown’s syndrome, for which there is even less data on saccadic behavior.

METHODS

Subjects

MR is a 51-year-old woman noted to have a right superior oblique palsy, presumed congenital given her denial of diplopia. She had a 4-diopter right hypertropia in primary position, which increased to more than 25 diopters in left gaze and to 10 diopters with right head tilt. There was excyclotropia of 5 degrees. Her vertical fusional amplitudes were large at 14 diopters. Other ocular motility was normal.

MS is a 40-year-old man who sustained a severe closed head injury and a right fourth nerve palsy in a motor vehicle accident 8 months prior to his visit. In primary position he had a 10 diopter right hypertropia and 10-diopter esotropia. The hypertropia increased to 25 diopters in left gaze and to 18 diopters in right head tilt. In downgaze, esotropia increased to 18 diopters and right hypertropia to 20 diopters. He did not have a left hypertropia in any position. He had 5 degrees of relative excyclotropia. He also had frequent square wave jerks and diffusely reduced pursuit gain, possibly on the basis of inattention. He had mild left hemiparesis and left infraorbital numbness.

ES is a 26-year-old medical student with left Brown’s syndrome diagnosed in childhood. She had moderately limited elevation of the OS, worse in adduction. She was orthotropic in primary position, and had a small right hypertropia in upgaze in the midline, which increased during rightward upgaze, but which switched to a small left hypertropia in leftward upgaze, suggesting bilateral restriction.

Two additional control subjects, age 31 and 42, with clinically normal eye movements were studied. All subjects gave informed consent according to a
protocol approved by the hospital's committee on clinical investigations.

Procedure and apparatus

Eye movements were recorded with the magnetic search coil technique, using 3-foot search coils (Crist Instruments, Baltimore, MD). Vertical and horizontal eye positions were sampled 500 times a second and velocity derived using a 7-point differentiation algorithm. The subjects sat in a chair facing a tangent screen upon which images were back-projected by an Eiki LC-7000U liquid crystal display projector. Subjects with abnormalities viewed the screen with their unaffected eyes patched. Stimuli, data collection, and data analyses were performed with a Power Macintosh 9600/233 computer, using the Vision Shell programming platform (MicroML, St Hyacinthe, Quebec).

The target was a small white annulus on a dark background. This was positioned along the horizontal meridian, either at screen center, 30 degrees left, or 30 degrees right. After an unpredictable interval of up to 2 seconds, the target jumped vertically between 5 and 40 degrees, in 5-degree steps and in random order. Only one direction was tested at a time, downward for superior oblique palsies and upward for Brown's syndrome. The goal was to generate a large array of centrifugal saccades spanning as complete a range of amplitudes as possible. Saccades in the midline, in adduction and in abduction were performed in blocks. 120 trials were performed in each block, generating over 200 saccades for each of the three horizontal gaze positions.

Analysis

All prior studies compared upward to downward saccades in their primary analysis. However, given the anatomy of the superior oblique, it is more logical to compare centrifugal saccades in adduction, versus those in abduction. We divided downward centrifugal saccades into amplitude bins of 5 degrees. Upward centrifugal saccades were divided into 4-degree amplitude bins, because of a smaller amplitude range. Our three primary variables were Peak velocity (PV), duration (D), and the peak velocity/mean velocity (PV/MV) ratio. This ratio, also formulated as (PVD)/A, expresses the relation between all three variables and is very uniform in normal subjects, around 1.6 (8). We plotted these variables as functions of amplitude. ANOVA was used for each subject's parameters to determine if there was a significant effect of lateral position on vertical saccade performance. We also used $t$ tests to compare data across bins between saccades in adduction and those in abduction. Because of the use of multiple $t$ tests with the bins, we set a higher cut-off for significance, at $P < 0.01$.

RESULTS

In the two normal subjects, there was no significant difference between saccades in adduction and those in abduction in any variable, for upward or downward saccades. The only exception was that the one subject had slightly faster upward saccades in adduction. This lack of difference for velocity is consistent with prior reports (4,6) (Fig. 1, 3).

FIG. 2. Superior oblique palsy: downward saccadic metrics. Conventions as in Figure 1. Top graphs are from patient MR, bottom graphs are from patient MS. Both patients have a consistent reduction in peak velocity and increase in duration for saccades in an adducted position.
Superior oblique paresis caused a significant reduction in peak velocity for downward saccades in adduction (MR: $P < 0.02$, MS: $P < 0.01$) (Fig. 2). In both MR and MS, this occurred mainly for saccades between 10 and 25 degrees in amplitude, where there was an average reduction of 18.6% in MR and 15% in MS. Saccadic duration was also significantly increased over this range (MR: $P < 0.06$, MS: $P < 0.03$). As a result, the PV/MV ratio was unaltered, indicating that the reduced force in generating peak velocity was reflected in a general and proportionate reduction in velocity across the entire saccade.

The data for superior oblique restriction was very different. Peak velocity did not differ between abducted and adducted positions for ES. However, in adduction the upward saccadic durations were increased in ES, leading to a striking elevation of the PV/MV ratio ($P < 0.02$) at almost all amplitudes (Fig. 4).

ES's data also revealed an unusual abnormality in saccadic trajectory, specific for saccades in the midline (Fig. 5). Centrifugal upward saccades, and to a lesser extent, centripetal upward and downward saccades, were often transiently interrupted by a slight reversal and simultaneous lateral shift of the eye, before resumption of their trajectory in a horizontally displaced position. Upward saccades were always shifted laterally, whereas downward saccades were always shifted medially. Prior to this dramatic shift, upward saccades were also found to have drifted slightly laterally. The peak velocities of the lateral component of these disruptive shifts were very rapid.

**FIG. 3.** Controls: Upward saccadic metrics. Conventions as in Figure 1. Control subject 1 had slightly increased peak velocities in adduction than did control subject 2. No other relations were significantly different.

**FIG. 4.** Brown's syndrome: upward saccadic metrics. Conventions as in Figure 1. There are trends to slightly faster and longer saccades in adduction. The net result is a highly significant increase in the PV/MV ratio.
ranging from 400 to 700 degrees per second (two to four times the normal velocity of about 200°/s for 5-degree saccades (9). These transient shifts were not tied to a specific orbital position.

**DISCUSSION**

Our data show that oblique muscle dysfunction can affect vertical saccadic velocities. Moreover, the effects of paresis are distinct from the effects of restriction. Superior oblique paresis reduced downward saccadic velocities. Upward peak velocities were not affected by restriction. In the patient with congenital Brown’s syndrome, restriction caused a disproportionate increase in upward saccadic duration, and hence a lowering of mean velocity relative to peak velocity.

A decrease in saccadic peak velocity is typical of many types of ocular motor paresis, both neuropathic and myopathic (10,11). The theoretical maximum contribution of the superior oblique to vertical eye movement is 18% (7), which should be achieved when the eye is adducted 30 degrees (1). Our finding that patients with severe superior oblique palsy have a 15–18% difference in the peak velocity of downward saccades performed in 30 degrees of abduction versus adduction fits this estimate precisely.

There are few studies of the effects of restrictive ocular motor disease on saccadic dynamics. Most investigators have examined Graves’ ophthalmopathy and have reported normal saccadic peak velocities, except in severe disease (12–15). One study did find reduced saccadic peak velocities (16). Graves’ disease is complicated, however, by the fact that it may affect extraocular muscle function with a combination of restriction and paresis (17). Nevertheless, most studies are consistent with our finding of normal peak velocities in Brown’s syndrome. Whereas some studies also comment on saccadic duration in Graves’ disease, none relates duration to peak velocity as we did with the PV/MV ratio. The PV/MV ratio found in ES indicates that restriction caused a subtle but disproportionate increase in duration,
implying, for a given amplitude and peak velocity, a decrease in mean velocity.

This finding has implications for our concepts of muscle restriction. One type of restriction may be a rigid obstruction to eye movement beyond a certain orbital position. One might expect that, after relatively unhindered motion to that point, a saccade would then be abruptly terminated. Peak velocity, which is usually achieved early in the course of a saccade (8), may not be affected, but amplitude and duration would be relatively reduced. Supernormal peak velocities would be the chief result. Because velocity would still be relatively high at the time of the sudden termination, it is also probable that mean velocity would remain relatively high, and the PV/MV ratio would be unaltered or even lowered for a given amplitude. Also, small saccades may not be affected if they do not cause the eye to reach the limiting orbital position.

On the other hand, with a more elastic restriction, passive resistive forces would gradually escalate during a saccade as the eye reached positions of greater eccentricity. Again, the early peak of velocity would not be affected, but the gradual braking effect of the elastic forces would reduce terminal velocity and prolong the final phase of the saccade. The result would be a reduction in mean velocity relative to peak velocity, as we found in ES.

Our patient with Brown’s syndrome had unusual ‘horizontal flips’ during vertical saccades. These were lateral during upgaze and medial during downgaze, and were accompanied by transient interruptions in the vertical trajectory. The speed of the horizontal movements was too fast for voluntary saccades. These movements are consistent with a sudden passive release from resistance. This finding might be analogous to the vertical shifts in Duane’s syndrome, where co-contraction of the horizontal recti causes the eye to ‘flip’ vertically during horizontal movements, mainly in a plane above the meridian (18,19). Here the restriction of the superior oblique combined with the contraction of the inferior oblique may generate a similar ‘bridle effect’ when the eye is moving in a vertical plane just lateral to the plane of maximal vertical function of the obliques. However, this would not explain the equally rapid medial deviations during downgaze. Another possibility is that an upward saccade stretches taut a short superior oblique tendon, until the tendon is nearly tangential to the globe and can slip around it with an abducting jerk. With a downward saccade from upgaze, the tendon would also have to slip back, with the eye rolling medially. Dynamic orbital MRI or ultrasound may help explore this issue in future patients.

REFERENCES
Patterns of Extraocular Muscle Weakness in Vasculopathic Pupil-Sparing, Incomplete Third Nerve Palsy

Scott Sanders, MD, Aki Kawasaki, MD, and Valerie A. Purvin, MD

Objective: To determine the pattern of extraocular muscle (EOM) paresis in incomplete vasculopathic third nerve palsies (3NP) that have normal pupillary function.

Methods: A retrospective study in a private practice and academic neuro-ophthalmic practice. Patients diagnosed with vasculopathic 3NP within 4 weeks of symptom onset were identified. The chart of each patient was reviewed to determine pupillary function and the pattern and degree of EOM and levator palpebrae paresis at the time of presentation.

Results: Of 55 patients with vasculopathic 3NP, 42 (76%) had normal pupillary function. Of these 42, 23 (55%) demonstrated an incomplete EOM palsy, defined as partially reduced ductions affecting all third nerve-innervated EOMs and levator (diffuse pattern) or partially reduced ductions that involved only some third nerve-innervated EOMs and levator (focal pattern). Twenty (87%) of these 23 patients showed a diffuse pattern of paresis; only three (13%) showed a focal pattern of paresis, one that affected only the superior rectus and levator muscles (superior division weakness).

Conclusions: Based on our series, most patients with EOM/levator involvement in pupil-sparing, incomplete 3NP of vasculopathic origin have a diffuse pattern of paresis. In contrast, our review of the literature suggests that pupil-sparing 3NP of aneurysmal origin usually have a focal pattern of paresis. We propose that distinguishing these two patterns of EOM paresis may be helpful in differentiating between aneurysmal and vasculopathic 3NP. Future studies will be needed to confirm the clinical utility of this hypothesis.

Key Words: Third nerve—Aneurysm—Vasculopathic palsy—Pupil sparing.

The two foremost diagnostic considerations in the evaluation of acute isolated third nerve palsy (3NP) are aneurysmal compression and ischemic injury (1). The former diagnosis is an acute medical emergency because of the possibility of aneurysmal rupture and intracranial hemorrhage. Urgent radiographic and neurosurgical evaluation is necessary. The latter diagnosis, also called vasculopathic 3NP, is a benign condition in which simple observation is sufficient because spontaneous recovery is the typical clinical outcome. Therefore, it is important to have a rapid and reliable clinical means of distinguishing between aneurysmal and vasculopathic 3NP.

In 1958, Rucker (2) provided one such clinical tool to differentiate these two entities when he wrote that “pupillary reactions yield valuable information. If they are normal the paralysis is probably due to occlusive vascular disease; if there is iridoplegia, paralysis is more likely due to an aneurysm.” In the setting of an acute isolated 3NP, the presence of a dilated or poorly reactive pupil warns the clinician of the possibility of an aneurysm and thus the need for acute evaluation. This came to be known as “the rule of the pupil,” and it has proved useful over the years (2–4). However, exceptions to the rule subsequently emerged in which patients with pupil-sparing, in fact, harbored an aneurysm (5–11). On closer inspection of these cases, it was noted that when the pupil was spared, other extraocular muscles were spared as well. Thus, the concept of “the exception to the rule” was proposed, stating that when the external ophthalmoplegia and ptosis related to 3NP are not complete, the presence of normal pupillary reactivity does not reliably exclude aneurysmal compression (12,13). In this setting, it has been suggested that a full neuroradiologic investigation including angiography be undertaken to exclude aneurysm. We sought to identify other clinical parameters that might assist the clinician in differentiating aneurysmal from vasculopathic 3NP when the palsy is incomplete.

We hypothesized that ischemic third nerve injury might produce a pattern of incomplete extraocular
EXTRAOCULAR WEAKNESS IN THIRD NERVE PALSY

Muscle (EOM) weakness that was distinct from that caused by aneurysmal compression. To this end, we retrospectively investigated the distribution and degree of EOM and levator palpebrae paresis among patients with incomplete, pupil-sparing vasculopathic 3NP.

SUBJECTS AND METHODS

The records of all patients diagnosed with acute vasculopathic 3NP at a single neuro-ophthalmology clinic over the past 14 years were reviewed. Patients who were not seen within 4 weeks of onset of symptoms were excluded because after that time interval, spontaneous recovery of function from ischemic injury may occur. Patients who had had strabismus surgery or mechanical iris dysfunction or were using topical ophthalmic medications that might alter pupillary function were excluded.

Based on the initial examination, the following three aspects of the clinical examination were documented: 1) the pupil size and reactivity; 2) paresis of the superior rectus, inferior rectus, medial rectus, inferior oblique, and levator palpebrae muscles; and 3) the degree of paresis of affected EOMs. For purposes of this study, EOMs refer to all third nerve-inervated striated muscles including the levator palpebrae.

We defined pupillary involvement as a poor pupillary light reaction on the side of the 3NP compared with the contralateral side and/or anisocoria that was notably worse under bright than dim light and in which the larger pupil was on the side of the 3NP. We defined levator palpebrae involvement as upper lid ptosis of 2 mm or more in the primary position with a demonstrable decrease in levator function. We defined EOM paresis as reduced ocular ductions, ocular misalignment, and saccadic slowing of the suspected paretic EOM. The degree of EOM paresis was classified as either complete (ductions completely abolished) or incomplete (ductions incompletely abolished). We subdivided incomplete palsy into two patterns: 1) diffuse, when all EOMs were paretic but incompletely so and 2) focal, when only some but not all the EOMs were paretic.

A diagnosis of vasculopathic origin was given to patients who had an acute isolated 3NP and complete spontaneous recovery over 3 months and had a history of one or more of the following: age greater than 50 years, hypertension, diabetes mellitus, and hyperlipidemia. Other causes of 3NP were excluded by history, physical examination, blood tests, edrophonium test, and neuromaging in appropriate patients. No patient demonstrated aberrant regeneration of the oculomotor nerve acutely or at follow-up.

RESULTS

Fifty-eight instances of vasculopathic 3NP in 57 patients were identified. Three instances (in two patients) were excluded because of surgically altered pupils or the use of topical medications that could affect pupillary function. Therefore, 55 patients with vasculopathic 3NP constituted the population of our study. Ages ranged from 40 to 86 years with a mean of 66.5 years. Thirty-seven were men (67%) and 18 were women (33%). The interval from onset of symptoms to time of clinical presentation ranged from 2 to 28 days with a mean of 13.4 days. Twenty patients underwent computed axial tomography, 28 patients had magnetic resonance imaging, and seven patients had both studies. Eleven patients had magnetic resonance angiography, 13 patients had catheter angiography, and two patients had both. All neuromaging tests were unremarkable except for one patient who had a remote occipital lobe infarction.

At the time of initial examination, 42 patients (76%) had normal pupillary function and 13 patients (24%) had abnormal pupillary function. Of the 42 patients with pupil-sparing, 19 (45%) patients had complete EOM paralysis and 23 patients (55%) had incomplete EOM paresis (Table 1).

These 23 patients with incomplete, pupil-sparing 3NPs constituted the specific subgroup of interest in this study. They accounted for 55% of our total population of vasculopathic 3NPs. Twenty of these 23 patients (87%) had paresis of all the EOMs, but the weakness was incomplete (diffuse pattern of paresis). Three patients (13%) demonstrated paresis of only the SR and levator palpebrae (superior division) muscles with sparing of the remaining EOMs (focal pattern of paresis). Reexamination of these three patients in subsequent weeks showed no change in the pattern of EOM paresis until recovery.

Because of concern regarding possible evolution of EOM weakness, the data were reanalyzed based on the timing of the first examination. Specifically, patients with partial, pupil-sparing 3NP seen within the first 10 days of onset of symptoms were analyzed separately, and their data were compared with the data from the entire group of similar patients. We found that 14 (61%) of 23 patients had been examined within 10 days of symptom onset; 12 (85%) had diffuse paresis, and two (15%) had focal paresis.

COMMENT

It is well established that in 3NP owing to compression by a posterior communicating artery aneurysm, the pupil is typically involved (2-4). Impairment of pupillary function is found in 86% to 95% of such patients, and, thus, pupillary examination and utilization of the "rule of the pupil" have been a critical step in the evaluation of an acute isolated 3NP (7,13). The high incidence of pupillary involvement is presumably related to the peripheral location of pupillary fibers within the oculomotor nerve.

TABLE 1. Characteristics of vasculopathic third nerve palsy in 55 patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil abnormal</td>
<td>13 (24%)</td>
</tr>
<tr>
<td>Pupil normal</td>
<td>42 (76%)</td>
</tr>
<tr>
<td>Complete EOM Palsy</td>
<td>19 (45%)</td>
</tr>
<tr>
<td>Incomplete EOM Palsy</td>
<td>23 (55%)</td>
</tr>
<tr>
<td>Diffuse Pattern</td>
<td>20</td>
</tr>
<tr>
<td>Focal Pattern</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
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</table>
making them particularly susceptible to extrinsic compression (14).

In 1985, Trobe (12) pointed out that in previously reported cases of aneurysmal 3NP in which the pupil was normal, the EOM palsy was incomplete. In other words, in cases with an incomplete 3NP, pupil sparing could not safely rule out the possibility of aneurysm. In his follow-up editorial outlining several "footnotes to the pupil rule," Trobe advised: "do not apply the rule when the extraocular pupil is incomplete. If some but not all of the oculomotor-innervated muscles are completely impaired or if all of the muscles are impaired but only slightly, then pupil sparing may exist with aneurysm..." (13). However, since then, there has been no further elaboration regarding any potential clinical significance to the difference between these two patterns of incomplete 3NP.

We wondered whether the pattern of EOM palsy might be helpful in determining the cause of a partial 3NP. More specifically, could the pattern of EOM palsy suggest whether aneurysmal compression or ischemic injury was the cause? To further investigate this, we studied the pattern of EOM palsy in patients with vasculopathic incomplete 3NP. We found that 20 (87%) of 23 patients with pupil-sparing, partial 3NP demonstrated a diffuse pattern of EOM palsy in which all the EOMs were paretic but only partly so. Three patients demonstrated a focal pattern of paresis in which some of the EOMs were weak but others were spared. From our data, the diffuse pattern of EOM paresis appears to be the predominant form of pupil-sparing, incomplete 3NP of ischemic origin.

In comparison, what is the predominant pattern of EOM weakness in patients with aneurysmal 3NP? To our knowledge, there is no comparable systematic analysis of patterns of EOM involvement in aneurysmal pupil-sparing 3NP. We therefore extracted individual case reports from the literature. Kissel et al. (7) described 51 patients in whom 3NP was the initial manifestation of a posterior communicating artery aneurysm. Of these patients, seven (14%) had a pupil-sparing 3NP at presentation and in all seven, the 3NP was incomplete. These authors defined incomplete as "greater than 2 mm of ptosis, decreased range of motion in the appropriate direction with or without deviation of the eye in the primary position, or a combination of these." There were no further specifics regarding the pattern of EOM paresis. Bartleson et al. (11) reported the ocular motor findings in 12 patients with incomplete 3NP owing to posterior communicating artery aneurysm. Nine of the 12 patients had initial pupillary impairment, but three patients remained who had a pupil-sparing, incomplete 3NP. Two of these patients had only ptosis and symptomatic diplopia, and one patient was described as having "paresis of R N-III EOMs and ptosis." Good (9) and Greenspan and Reeves (10) have each reported a single case of piosis as the sole sign of 3NP owing to a similarly located aneurysm. Because the percentage of aneurysmal 3NP that spares the pupil is small, a large series is difficult to achieve. Based on the cases cited here, it appears that the focal pattern of EOM paresis may be the more predominant form of pupil-sparing, partial 3NP when owing to aneurysm.

We examined some potential sources of error for our findings. First, we acknowledge that the diagnosis of a vasculopathic cranial neuropathy is a clinical one and thus, it is possible that our patient population inadvertently contained patients with other causes of 3NP such as inflammatory disease. Second, because we included patients examined as late as 4 weeks from symptom onset, we acknowledge that a focal pattern of EOM paresis might have been missed. Because Jacobson and Brust (14) observed that the peak severity of ophthalmoplegia in patients with ischemic oculomotor palsies occurred at a median of 10 days, we reanalyzed our data by reviewing those patients who were examined within the first 10 days of symptom onset (early group, n = 14) and compared the results with those from the entire group of patients with incomplete, pupil-sparing 3NPs seen within the first 4 weeks (n = 23). Two of 14 patients (15%) of the early group had focal EOM paresis compared with 13% of the entire group. Furthermore, at subsequent follow-up, the pattern of EOM paresis in these two patients did not progress to involve other muscles before spontaneous recovery occurred. Because the findings in the two groups were quite similar, we believe that it is valid to draw conclusions from the entire patient group.

Third, we recognize that our hypothesis regarding two different patterns of partial EOM paresis based on two different etiologies lacks comparable data for patients with aneurysmal palsy. We remind the reader that our data for vasculopathic palsy represents just half of that hypothesis. The full implication of our data awaits a better description of the pattern of EOM paresis in aneurysmal palsy.

Where in the overall evaluation of an acute 3NP might our findings be helpful? In patients with a 3NP in whom the pupil is dilated or poorly reactive, the evaluation is generally straightforward; these patients should undergo timely and appropriate investigation for a possible aneurysm. Likewise, there is little controversy regarding observational management of cases in which pupillary function is normal but EOM palsy is incomplete, as these are likely vasculopathic. These clinical scenarios conform to the "rule of the pupil" (12,13). The problematic clinical scenario occurs when pupillary function is normal and EOM palsy is incomplete. In such cases, the "rule of the pupil" has been found to be less reliable, and it is in this setting that we believe a diffuse pattern might, if future studies bear us out, tilt the physician toward suspecting a vasculopathic rather than an aneurysmal cause.

REFERENCES

EXTRAOCULAR WEAKNESS IN THIRD NERVE Palsy

Catastrophic Antiphospholipid Antibody Syndrome Manifesting as an Orbital Ischemic Syndrome

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Painful bilateral ophthalmoparesis, marked proptosis, increased intracranial pressure, and blindness developed in a 29-year-old woman with protein C deficiency and catastrophic antiphospholipid syndrome. Magnetic resonance imaging of the orbits showed bilateral proptosis, globe tenting, and tethering of the optic nerves consistent with an orbital ischemic syndrome. Despite aggressive therapy for antiphospholipid syndrome, the patient died. The autopsy showed necrosis of orbital tissues. This is the first report of orbital ischemic syndrome from protein C deficiency and antiphospholipid syndrome.

Key Words: Antiphospholipid antibody syndrome—Orbital ischemic syndrome.

Antiphospholipid syndrome (APS), first recognized in patients with systemic lupus erythematosus and later in patients without systemic lupus erythematosus or underlying autoimmune disease, is associated with venous and arterial thrombosis (1, 2). Antiphospholipid syndrome may involve vital organs with life-threatening consequences ("catastrophic APS") (2). This report describes a patient with protein C deficiency and catastrophic APS in whom an orbital ischemic syndrome developed.

CASE REPORT

In 1993, a 29-year-old woman with deep-vein thrombosis, hematuria, and a history of two spontaneous abortions showed an increased anticardiolipin antibody immunoglobulin (Ig) G level of 32.2 GPL (<23) and IgM of 2.8 MPL (<11). Antinuclear antibody test results were negative. She had no history of migraine, transient ischemic attacks, or joint pain.

Skin necrosis developed after the patient was treated with warfarin, so this drug was withheld. She was treated instead with oral prednisone and subcutaneous heparin. Serum test results showed a low protein C activity of 22% (70-160%) and a normal protein S activity of 80% (65-140%).

In 1998, the patient began to experience episodes of painful unilateral proptosis involving either eye without visual loss. She was treated successfully each time with intravenous and oral corticosteroids for a presumptive diagnosis of idiopathic inflammatory orbitopathy.

In January 2000, a large, nonhealing ulceration developed on the patient's right lower extremity, and she was admitted to the hospital. Multiple erythematous skin lesions also developed. A skin biopsy of the right arm showed extensive vascular thrombosis and neutrophilic infiltrate around but not within blood vessels. During this time, right periocular pain and proptosis with substantial visual loss developed, and the patient again responded completely to corticosteroids. A gadolinium-enhanced orbital magnetic resonance imaging scan showed enhancement of the sclera, fat, and the optic nerve sheath in the right orbit. After being discharged from the hospital, the patient was treated with subcutaneous heparin and oral corticosteroids for maintenance.

In March 2000, chronic renal insufficiency, hematuria, sepsis, and pneumonia developed, and the patient was admitted to the hospital. The right lower extremity ulceration was still present. She was treated with bladder irrigation and intravenous vancomycin for a diagnosis of enterococcus sepsis. Protein C activity was again low at 20% (70-160%). Anti-β2-glycoprotein I IgG and IgA levels were increased at 21.82 G units (normal, <20 G units) and 24.82 A units (normal, <20 A units), respectively. The anti-β2-glycoprotein IgM level was normal, as were antiphosphatidylserine test results. Antinuclear
antibody testing and anti-DNA testing yielded negative results. C3 complement level was increased at 101.9 mg/dl (50–100 mg/dl), and C4 complement level was increased at 48 mg/dl (12.5–45 mg/dl). Cryoglobulin testing yielded negative results. The patient was discharged from the hospital in May 2000, and subcutaneous heparin and a slow taper of oral corticosteroids were prescribed.

In June 2000, the patient presented with bilateral painful proptosis and visual loss. She was drowsy but oriented. Her blood pressure was 153/94 mm Hg, her pulse was regular at 80 beats/minute, and she was afebrile. She had no light perception vision OU, and the pupils were fixed at 5 mm OU. She had total ophthalmoplegia bilaterally and bloody epiphora from extensive hemorrhagic chemosis. Trigeminal and facial nerve function was intact. Marked corneal edema prevented detailed visualization of the anterior chamber, and there was no view of the fundus. Tonopen intraocular pressures were 39 mm Hg OD and 47 mm Hg OS. She had no weakness or numbness of the extremities. A large, nonhealing ulceration was present on the right lower extremity.

A magnetic resonance imaging scan of the brain and orbits showed bilateral proptosis and tethering of the optic nerves, such that both globes were oval (tented) (Fig. 1). There was no enhancement of orbital tissues, presumably because of necrosis. The brain appeared to be normal.

Intravenous methylprednisolone, 125 mg four times daily, was initiated. Bilateral canthotomy and cantholysis reduced the intraocular pressures to 22 mm Hg OD and 23 mm Hg OS without improvement in vision. The patient underwent an endoscopic bilateral medial and inferior orbital wall decompression with further improvement of the intraocular pressures but no change in visual acuity. Under the surgical microscope, shallow chambers and microhyphemas were visible OU. An echocardiogram showed a 3 x 2-cm thrombus in the right atrium. A carotid Doppler study yielded normal results.

A diagnosis of orbital ischemic syndrome secondary to catastrophic APS and protein C deficiency was made. Plasmapheresis treatment was rejected because of high risk in view of the cardiac thrombus, and intravenous Ig treatment was rejected as too nephrotoxic, considering the patient’s renal insufficiency.

Later, in June 2000, the patient experienced acute respiratory arrest and hypotension. She underwent intubation and was transferred to the intensive care unit. Vasocostricators were initiated. Endoscopy showed a gastric ulcer without hemorrhage. An abdominal computed tomography scan showed a large subcapsular hematoma of the liver. Computed tomography of the brain showed bilateral proptosis but no intracranial abnormality. A ventilation/perfusion scan showed a low probability for a pulmonary embolism. The hemoglobin and hematocrit levels continued to decrease. Complete renal failure developed. Dialysis caused a further decrease in blood pressure. The patient died several days later, presumably of multiorgan failure.

AUTOPSY

Autopsy showed a massive intra-abdominal hemorrhage with 4 L of blood and clot, a large hematoma of the liver, and infarctions of the lung, pancreas, and bladder. The adrenal glands were atrophic. The kidneys showed glomerulosclerosis and interstitial nephritis. The heart had a large right atrial thrombus. Gross examination of the orbital tissues showed marked enlargement and hemorrhage of the extraocular muscles. The conjunctiva was markedly hemorrhagic and edematous, and the corneas were diffusely cloudy. The eyes were opened vertically in an anteroposterior direction, revealing an enlarged lens with opacification, cloudy, hemorrhagic vitreous fluid, and sloughing of the retina and retinal pigment epithelium. The globes were conical in shape because of flattening postequatorially (Fig. 2). Microscopic examination showed near-complete coagulative necrosis of all intraocular tissues, with vascular congestion and intravascular fibrin thrombi (Fig. 3). The retinas were almost entirely necrotic, with a single peripapillary focus of retained nuclear architecture. The extraocular muscles showed marked vascular congestion, hemorrhage, coagulative necrosis, and intravascular fibrin thrombi.

DISCUSSION

Antiphospholipid syndrome manifests as recurrent fetal loss thrombocytopenia and as venous and arterial
thrombosis of the skin, brain, retina, heart, lungs, liver, and kidneys (1,2). Patients have increased titers of antiphospholipid antibodies, a heterogeneous group of IgM and IgG autoantibodies against protein and phospholipid complexes (3). The thrombotic tendency is paradoxical because in vitro, there is prolongation of phospholipid-dependent coagulation assays (3). In primary APS, there are no associated autoimmune diseases, such as systemic lupus erythematosus (1), as in our patient.

Catastrophic APS denotes a potentially life-threatening course over days to weeks (2). A seminal paper by Asherson et al. (2) in 1998 outlined key points about catastrophic APS. Spontaneous fetal abortions were present in 24% of patients. Sixty-six percent were women, and 56% had primary APS. Fourteen percent had nonhealing lower extremity skin ulcerations, and 78% had kidney involvement. Cardiac involvement was present in 50%, 2% of which had an intracardiac thrombus. Central nervous involvement was present in 56%. Fourteen percent of patients had retinal vascular involvement.

Ophthalmologic involvement in APS includes transient monocular blindness (4), vaso-occlusive retinopathy (cotton wool spots with or without retinal hemorrhages), branch retinal artery, central retinal artery or central retinal vein occlusion (5), and choroidal capillary vessel occlusion (1). Iritis, scleritis and keratitis, viretritis, retinal detachment, and posterior scleritis (6) ocular ischemia and migraine-like disturbances have also been reported (7).

Confusion in diagnosis of APS may arise because coagulation studies can be influenced by treatment with warfarin or heparin. For example, protein C and S values are both decreased in patients receiving warfarin but are not influenced by heparin. Antithrombin III is decreased in patients receiving heparin but not warfarin. Lupus anticoagulant test results can be falsely positive after warfarin or heparin therapy; antiphospholipid antibody values are not influenced by either drug (8). Of the antiphospholipid antibody isotypes, IgG confers the greatest risk of thrombosis when compared with IgM, and some authors believe thrombocytopenia is an important risk factor (9). Our patient had increases of both antiphospholipid antibody isotypes and a low protein C level at a time when she was not being treated with warfarin.

Proposed pathophysiologic mechanisms of APS vary and include stimulation of platelet aggregation, damage to vascular endothelial cells, and interference with protein C or antithrombin III pathways (10). Another theory states that thrombogenesis may rely on an anionic phospholipid called annexin-V. This protein has potent anticoagulant activity and exists on phospholipid surfaces at the vascular-blood interface. It plays a thrombo-regulatory role by preventing anionic phospholipids from complexing with circulating coagulation proteins. There is some experimental evidence that annexin-V is reduced in patients with antiphospholipid antibodies (10). However, this theory has been debated (11) and disputed experimentally (12). In addition to antiphospholipid antibodies and protein C deficiency, our patient also tested positive for antibodies to β2-glycoprotein I, a phospholipid-binding protein. Patients with APS have autoantibodies that react to phospholipids on β2-glycoprotein I (13). The presence of this antibody is significantly associated with features of APS and thrombosis (14). β2-Glycoprotein acts as a phospholipid-bound natural anticoagulant by clearing anionic procoagulant phospholipids from the circulation. Interference with β2-glycoprotein I leads to a hypercoagulable state (13).

Fifty percent of patients with catastrophic APS die (2). Treatment with a combination of anticoagulation, corticosteroids, plasmapheresis, or intravenous Ig allows recovery in 70% of patients (2).

Our patient is unique in having orbital involvement. Orbital ischemic syndrome has been reported with orbital trauma (15), carotid dissection (16), subperiosteal abscess (17), giant-cell arteritis, and mucormycosis (18). The globe tenting noted on our patient's orbital magnetic resonance imaging scan (Fig. 1) is a well-recognized sign of increased orbital tension. If the angle of the posterior pole tenting is less than 120°, as in our patient, emergent surgical decompression is recommended (17). Perhaps the episodes of orbital pseudotumor in our patient were a milder form of orbital ischemia from the hypercoagulable state. The additive effects of the protein C deficiency and antiphospholipid antibodies increased the risk for thrombosis. To our knowledge, this is the first description of an orbital ischemic syndrome resulting from a combination of primary APS and protein C deficiency (1–18).

In summary, an orbital ischemic syndrome may result from a combination of APS and protein C deficiency. A patient with an orbital inflammatory syndrome, even if reversible, may suffer from this multiple hypercoagulable state. Globe tenting on cranial neuroimaging may be indicative of orbital ischemia from APS. If APS is diagnosed, early treatment may avoid catastrophic consequences.
REFERENCES

Seesaw Nystagmus Following Whole Brain Irradiation and Intrathecal Methotrexate

John A. Epstein, MD*, Mark L. Moster, MD†, and Michael Spiritos, MD‡

A patient developed pendular seesaw nystagmus (SSN) 14 months after receiving radiation and intrathecal methotrexate for intracranial spread of systemic lymphoma. The nystagmus followed severe visual loss from damage to the optic nerves and chiasm. This case expands the causes of pendular SSN and lends further support to the notion that focal midbrain lesions may not be a prerequisite for its development.

Key Words: Seesaw nystagmus—Radiation—Nystagmus—Lymphoma—Methotrexate.

Seesaw nystagmus (SSN) is a rare form of nystagmus characterized by alternating elevation and intorsion of one eye and simultaneous depression and extorsion of the opposite eye. Conditions associated with SSN include parasellar or suprasellar masses such as pituitary adenoma and craniopharyngioma, upper brain stem stroke, severe head trauma, septo-optic dysplasia, syringobulbia, Arnold Chiari malformations, multiple sclerosis, congenital achiasma, and loss of vision alone secondary to cone-rod dystrophy and retinitis pigmentosa (1). In many of these disorders, damage to the rostral brainstem has been demonstrated or presumed (2). However, the fact that congenital achiasma and cone-rod dystrophy can, by themselves, cause SSN, suggests that midbrain damage is not required to produce this nystagmus (3). We present a patient with radiation and chemotherapy-induced optic neuropathy and chiasmal involvement with SSN but without radiologic evidence of focal lesions in the brainstem.

CASE STUDY

A 64-year-old woman was diagnosed with diffuse large cell lymphoma of the pleura, mesentery and multiple bones and treated with 6 cycles of chemotherapy, including cyclophosphamide 1200 mg, vincristine 2 mg, and adriamycin 80 mg, followed by 4 doses of rituximab. Within one year of presentation, she developed seizures and right sixth and seventh nerve palsies. MRI revealed enhancement of the subependymal regions of the lateral ventricles and superior cerebellum, as well as focal meningeal enhancement of the right 7th and 8th nerve complex. Lumbar puncture revealed malignant lymphocytes. She received six 12-mg doses of intrathecal methotrexate (MTX) via Ommaya reservoir, and whole brain irradiation (XRT), 10 fractions of 300 cGy for a total of 3000 cGy. MRI two months later showed marked reduction in the CNS lesions.

Neuro-ophthalmologic examination was performed for a two-month history of progressive visual loss OS that occurred eight months after this treatment. Visual acuity was 20/20 OD and count fingers OS with a 2-3+ afferent pupillary defect, and trace optic pallor OS. Visual fields showed diffuse loss OS with hemianopic loss OD (Fig. 1). There was no nystagmus. MRI showed enhancement of the left side of the optic chiasm and both optic nerves, left greater than right (Fig. 2). Lumbar puncture revealed normal cerebrospinal fluid. The patient was diagnosed with optic neuropathy and chiasmopathy induced by radiation and, possibly, methotrexate.

After progressive worsening of vision OU, she was treated with Solumedrol 1 gm intravenously x2, 30 treatments of hyperbaric oxygen, and Coumadin (Bristol Myers Squibb, Princeton NJ). Visual acuity stabilized at 20/40 OD and hand motions OS. However, 4 months later, Coumadin was discontinued after she fractured her hip.

FIG. 1. Visual fields demonstrating diffuse loss OS with hemianopic loss OD.
SEESAW NYSTAGMUS FOLLOWING WHOLE BRAIN IRRADIATION

Two months after discontinuing Coumadin, her vision OD declined precipitously to 20/200 OD and hand motions OS. Pendular seesaw nystagmus in primary position was now noted. The patient was alert and had no focal neurological deficits suggestive of a midbrain lesion. Brain MRI, performed 18 months post XRT/MTX treatment, showed prominent periventricular white matter changes consistent with the effects of radiation and MTX, as well as atrophy of the optic chiasm and adjacent structures (Fig. 3).

DISCUSSION

Two patterns of SSN have been described: 1) Jerk SSN, associated with lesions in the region of the interstitial nucleus of Cajal (1), and 2) pendular SSN, associated with parasympathetic or chiasmal mass lesions (4). In the past, there has been the impression that sellar lesions caused pendular MRI by pressure on the midbrain (5). However, brainstem disease may not be a prerequisite to pendular SSN, as exemplified by many case reports of this form of nystagmus occurring in patients with retinitis pigmentosa or cone-rod dystrophy (3,6) and no clinical or imaging evidence of brain stem disease. Our case, which shows midbrain atrophy but no focal or clinical abnormalities referable to the brain stem, adds support to that concept. It has been proposed that visual loss inactivates the normal recalibration mechanism for eye movements during head tilt through a visual-vestibular pathway (2).

Although intrathecal chemotherapy with MTX and cytosine arabinoside has been abundantly reported to cause blindness and demyelination of the optic nerves and chiasm (7,8,9), no previous cases have described SSN. Our case adds radiation and MTX as a possible etiology for SSN and lends further support to the notion that imaging evidence of a focal midbrain lesion is not a prerequisite for SSN.

REFERENCES

Visual Function and Quality of Life Among Patients with Giant Cell (Temporal) Arteritis

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Objective: To investigate patient perception of visual and systemic disability associated with giant cell arteritis (GCA) and whether the perceived disability can be correlated with visual performance measures.

Methods: We prospectively evaluated and compared the visual performance and quality of life survey for 20 patients with GCA after 4 to 5 weeks of corticosteroid therapy and after one year of therapy. We measured visual acuity, contrast sensitivity, and threshold perimetry and patients completed the Activities of Daily Vision Scale (ADVS) and the short-form of the Health Survey (SF-36). The results were grouped by GCA affected or unaffected eye or by better or worse eye and reported as a decimal and percent impairment for acuity, log units for contrast, mean deviation and the Advanced Glaucoma Intervention Study (AGIS) score for perimetry. The results for patients with and without visual loss were compared. Correlation analyses between ADVS categories and visual performance measures, SF-36 categories and the presence of visual loss, total corticosteroid dose, systemic symptoms, secondary hypertension or diabetes mellitus, the presence of vertebral fracture, and visual performance were performed.

Results: Day driving was the only ADVS category significantly reduced at baseline in patients with visual loss (62.5) compared with those without visual loss (96.3, P = 0.04). Modest to moderate correlations between ADVS categories were most frequent for percent binocular acuity impairment with day driving ($r = -0.62, P = 0.017$), with distance vision ($r = -0.5, P = 0.02$), and with glare ($r = -0.59, P = 0.006$); and the AGIS score of the worse eye with day driving ($r = -0.66, P = 0.01$), with near vision ($r = -0.49, P = 0.03$), and with glare ($r = -0.48, P = 0.04$). The baseline SF-36 scores did not correlate with the presence of vision loss at baseline or systemic complications. The ADVS and SF-36 scores were similar at one year. The total dose of corticosteroids only had a modest correlation with the one-year mental health score ($r = -0.45, P = 0.05$), but there was no correlation between SF-36 scores and other systemic side effects of steroid therapy.

Conclusion: Except for the day driving score, the ADVS did not differ between patients with and without visual loss. The SF-36 did not distinguish between patients with and without visual loss and did not reveal significant trends. The ADVS and SF-36 did not reveal significant disability in GCA patients and there were no strong correlations with any visual performance or systemic measures.

Unless treatment with corticosteroids is begun early, visual loss, which is frequently severe, occurs in almost 50% of patients with giant cell arteritis (GCA). The inflammatory changes of the ophthalmic artery branches lead to ischemia of the orbital tissues and profound optic neuropathy, retinal and choroidal infarction, and less commonly ocular movement limitation (1-4). When a patient experiences monocular visual loss, corticosteroid therapy is initiated as soon as the diagnosis is suspected because in approximately 33% of untreated patients, the second eye will lose vision within several weeks (5). Unfortunately, the required long-term duration (typically 6 to 24 months) of treatment with corticosteroids can cause severe systemic complications (osteoporosis, gastric ulcer, diabetes, high blood pressure, immunosuppression, depression, weight gain) (6,7) and less often, ocular morbidity (cataract, glaucoma) (8-11). Thus, both the disease and the therapy can lead to significant visual, physical, social, and emotional functional disability.

The severity of disease and the effects of therapies on daily living activities can be evaluated using methods that have been used to evaluate patients perceived visual and global function disability in several ophthalmic disorders, including cataract, glaucoma, and retinal diseases (12,13,14). In applying this approach to patients with GCA several issues should be addressed.
1. Do patients with GCA cause visual loss have more visual impairment in daily activities than those without GCA associated visual loss?

2. At one year, after six to twelve months of corticosteroids, do patients with GCA have a change in their perceived visual, emotional, physical, or social functioning?

3. Does the GCA patient’s perceived visual disability correlate with accepted measures of visual function?

4. Does six to twelve months of corticosteroid therapy worsen the disability or create a systemic or ocular disorder that reduces the GCA patient’s perceived ability to function?

To answer these questions we assessed patients entered into a prospective clinical trial at three university medical center rheumatology and neuro-ophthalmology services. The primary goal of the study was to compare conventional corticosteroid therapy with a combination of methotrexate and corticosteroid treatment to address the question of disease control and rate of drug related complications. However, difficulties with recruitment precluded sufficient numbers to answer the question whether methotrexate is beneficial but the prospective collection of data on visual performance and quality of life measures has provided informative results.

PATIENTS AND METHODS

Inclusion criteria, clinical studies

Patients age more than 55 years with giant cell arteritis who met study criteria for diagnosis were entered into a randomized, prospective, placebo-controlled study. The criteria that is more exact than the classification of the American College or Rheumatology to ensure the inclusion of patients with GCA included:

1. Patients must have symptoms suggestive of GCA and a temporal artery biopsy (performed within one week of steroid initiation), with signs of panarteritis including chronic inflammatory cells, disruption of the internal elastic lamina, with or without giant cells, except for 2 or 3.

2. Patients with acute anterior or posterior ischemic optic neuropathy with symptoms suggestive of GCA, and ESR more than 60 mm/h (without other cause for elevated ESR, i.e., blood dyscrasia, lymphoma, tuberculosis, renal failure) even if negative temporal artery biopsy.

3. Patients with symptoms suggestive of GCA and pulseless disease with ESR more than 60 mm/h.

Patients were excluded if they had additional visual or systemic illnesses that contraindicated the use of corticosteroids or methotrexate or could complicate or bias the study. Twenty of the 22 patients participated in the quality of life evaluations with the two additional patients excluded because they did not have quality of life assessments at the baseline evaluation.

Patients with symptoms or signs of ophthalmic involvement were examined immediately prior to or after the onset of visual disturbance by MJK. Study baseline and all subsequent evaluations (1, 3, 6, and 12 months) included full ophthalmologic evaluation with best corrected visual acuity testing using Bailey-Lovie logMAR chart under standard conditions, contrast sensitivity testing using Peli-Robson charts under standard conditions (15), complete ophthalmologic examination, and visual field testing with the Humphrey 24-2 strategy.

For OU, the visual acuity was expressed as decimal (20/20 = 1.0, finger counting = 0.012, hand motion = 0.006, light perception = 0.001, no light perception = 0), the lowest contrast seen in log units of contrast, and the visual field threshold as mean deviation (MD). For each patient, the AMA guide to permanent impairment was used to determine a percent of central vision impairment for the eye with worse acuity and a percent binocular impairment for both eyes using the visual acuity (17). In addition, the visual fields were scored using the AGIS scoring system (18).

All patients initially received daily corticosteroid therapy (range from 40 mg to 1000 mg) after diagnosis as determined by the patient’s physician and the severity of the disease. Over four to five weeks the daily steroid dose was reached to the equivalence of 30 to 40 mg of prednisone at which time (baseline) each patient was entered into the study. The suggested regimen for subsequent prednisone therapy included a gradual reduction by 5 mg per week until attaining 20 mg daily at the end of the second month followed by tapering by 2.5 mg per week until the drug was completely suspended or symptoms or signs of a relapse occurred that were unresponsive to changing the study drug (methotrexate or placebo).

At baseline, patients were randomized to the addition of either oral placebo or methotrexate of 10 mg per week to the daily steroid dose. If a relapse occurred and no sign of drug toxicity existed, the study drug, not the prednisone, was to be increased. At one year, if a remission was achieved, the study drug was to be reduced until it was completely withdrawn. There were 11 patients in the methotrexate group and nine patients in the placebo group. Patients in both groups received comparable initial doses and total cumulative doses at one year (mean 6,184 mg, SD 2,048 for methotrexate group, mean 5,436 mg, SD 1,600 for placebo group, P = 0.39) of prednisone.

All patients received 1500 mg/d of calcium carbonate and 400 IU of vitamin D to prevent osteoporosis, folic acid 1 mg orally each day, an H-2 blocking agent or carafate 1 g daily to prevent gastrointestinal ulceration. After additional drugs to prevent osteoporosis became available, seven patients received one of these agents, usually after several months of starting steroids. When necessary, the appropriate agent was added to control blood pressure or blood glucose. Radiographs were taken of the spine and hip at baseline and at one year to determine the prevalence of fractures after one year of corticosteroid therapy.
Quality of life measurements

At baseline and at each visit, in addition to a standardized examination, patients were asked whether they experienced any of these nine symptoms of GCA: jaw claudication, polymyalgia rheumatica, tongue claudication, fever, ischemia of the extremities, headache, malaise, unintentional weight loss, loss of appetite. We also prospectively documented the new onset or significant worsening of diabetes mellitus, systemic hypertension, hip and vertebral fractures, or osteoporosis in the hip and spine.

At baseline and at one year, patients were administered a quality of life assessment in person or by telephone by the clinical coordinator (RL) who was blinded to the patients’ medications. The first part of the questionnaire was the SF-36 Health Survey (19,20), which assesses 8 areas; limitations in physical function (PF), social function (SF), or usual role activities due to health problems (RP), bodily pain (BP), limitation in usual role due to emotional problems (RE, emotional role), vitality (VT), general health (GH), and mental health (MH). The second part of the questionnaire used the Activities of Daily Vision Scale (ADVS) developed by Mangione et al. (21,22) These questions asked about the individuals’ ability to perform night driving (ND), day driving (DD), see at distance (DV) and near (NV), and handle glare (GL).

Data analysis

The values for ADVS (21,22) and SF-36 (19,20) categories were normalized. Higher scores suggested better visual and daily living functioning. Because there was no difference for the ADVS or SF-36 scores between the placebo and methotrexate treated patients, their data are reported together. Data were grouped by the presence or absence of GCA associated visual loss. Data from the one patient with congenital vision loss in one eye and no GCA caused vision loss were grouped with the patients without GCA loss (in fact, the baseline ADVS and SF-36 scores were approximately at the median for the scores obtained from the patients without GCA vision loss). The data were analyzed to determine whether patients with GCA visual loss had quality of life scores significantly different than patients without visual loss and whether the quality of life measures at one year changed after treatment with steroids. The mean for the five categories of ADVS and for eight categories of the SF-36 at baseline and at one year were compared for all patients using the t test and for patients with visual loss and patients without visual loss using the Wilcoxon signed-rank test (23). We also determined the 95% confidence intervals for each ADVS category for patients with and without visual loss.

The baseline visual acuity, contrast sensitivity, mean deviation and AGIS score for the worse eye and the visual acuity, mean deviation and AGIS score for the better eye for each patient, the percent central vision impairment of the worse eye, and the percent binocular central impairment for each patient were correlated with each of the five categories of the ADVS using the Spearman rank correlation method (23).

The Spearman rank correlation was used to evaluate the number of GCA symptoms, the various visual performance parameters at baseline with the baseline score in each baseline SF-36 category and the total cumulative dose of corticosteroid, hypertension, diabetes mellitus, and hip or vertebral fracture at one year with the score in each one-year SF-36 category. There were too few systemic GCA symptoms at one year to measure a potential correlation with the SF-36 scores.

For all correlation values, only values with a P value less than 0.05 were considered significant with relationships categorized as weak (r < 0.32), modest (r = 0.32 to 0.55), moderate (r > 0.55 to 0.75), or strong (r > 0.75).

RESULTS

Baseline vision

GCA caused visual loss (anterior ischemic optic neuropathy or central retinal artery occlusion) was present at baseline in five eyes of four patients; the other 16 GCA patients had no ischemic visual loss (Table 1). One patient in the group without GCA visual loss had one eye with a congenital toxoplasmosis maculopathy and a visual acuity of 0.05. The remainder of the eyes had minimal or no visual performance abnormalities secondary to baseline cataract, glaucoma, age related maculopathy.

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**TABLE 1. Baseline visual performance**

<table>
<thead>
<tr>
<th></th>
<th>Worse eye acuity</th>
<th>Better eye acuity</th>
<th>Worse eye contrast log units</th>
<th>Better eye contrast log units</th>
<th>Worse eye MD (db)</th>
<th>Better eye MD (db)</th>
<th>Central impairment worse eye, %</th>
<th>Binocular impairment, %</th>
<th>Worse eye AGIS</th>
<th>Better eye AGIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with no visual loss, mean</td>
<td>0.71</td>
<td>1.11</td>
<td>1.36</td>
<td>1.43</td>
<td>-5.87</td>
<td>-390</td>
<td>12.1</td>
<td>4.4</td>
<td>5.14</td>
<td>2.36</td>
</tr>
<tr>
<td>SD</td>
<td>0.27</td>
<td>0.35</td>
<td>0.31</td>
<td>0.31</td>
<td>2.40</td>
<td>2.72</td>
<td>23.3</td>
<td>6.1</td>
<td>0.57</td>
<td>1.18</td>
</tr>
<tr>
<td>Patients with visual loss, mean</td>
<td>0.21</td>
<td>1.64</td>
<td>0.24</td>
<td>1.26*</td>
<td>-24.38</td>
<td>-7.94*</td>
<td>78.8</td>
<td>27.7</td>
<td>15.8</td>
<td>6.4*</td>
</tr>
<tr>
<td>SD</td>
<td>0.30</td>
<td>0.41</td>
<td>0.39</td>
<td>0.26</td>
<td>8.44</td>
<td>9.83</td>
<td>37.9</td>
<td>22.1</td>
<td>6.94</td>
<td>6.71</td>
</tr>
<tr>
<td>P</td>
<td>0.004</td>
<td>0.0001</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.19</td>
<td>0.0003</td>
<td>0.002</td>
<td>0.0002</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

*Includes the results from the less-affected eye in the case of bilateral GCA ischemia, with visual acuity of 0.2, MD (mean deviation) = -26.9, contrast sensitivity 1.0 log units, and AGIS (Advanced Glaucoma Intervention Study) score of 19.

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There was no particular symptom that was significantly more prevalent in either group. In particular, 3 of 5 patients with vision loss and 6 of 15 patients without vision loss had jaw claudication.

**Baseline quality of life measures and correlations**

Patients with and without GCA visual loss averaged three other symptoms of systemic GCA (Tables 2 and 3, Figs. 1 and 2). There was no particular symptom that was significantly more prevalent in either group. In particular, 3 of 5 patients with vision loss and 6 of 15 patients without vision loss had jaw claudication.

**TABLE 2. Comparison of ADVS in patients with and without vision loss at baseline and one year**

<table>
<thead>
<tr>
<th></th>
<th>Night driving Mean, SD</th>
<th>Day driving Mean, SD</th>
<th>Distance vision Mean, SD</th>
<th>Near vision Mean, SD</th>
<th>Glare Mean, SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, cases vision loss</td>
<td>60.0, 28.8</td>
<td>62.5, 34.6</td>
<td>71.2, 26.4</td>
<td>70.8, 31.5</td>
<td>51.2, 26.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.0–100.0</td>
<td>14.5–110.5</td>
<td>34.9–107.4</td>
<td>27.0–114.5</td>
<td>14.7–87.8</td>
</tr>
<tr>
<td>Baseline, no vision loss</td>
<td>77.6, 28.0</td>
<td>96.3, 10.5</td>
<td>86.2, 16.8</td>
<td>96.5, 4.4</td>
<td>85.1, 14.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>55.0–100.0</td>
<td>11.3–115.4</td>
<td>28.8–109.4</td>
<td>35.6–96.2</td>
<td>39.4–99.6</td>
</tr>
<tr>
<td>Baseline, no vision loss vs cases with vision loss,</td>
<td></td>
<td>96.3 vs 62.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.04</td>
<td>0.42</td>
<td>0.22</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>One year, cases vision loss</td>
<td>563.3, 32.7</td>
<td>63.3, 37.5</td>
<td>69.2, 29.1</td>
<td>65.9, 21.8</td>
<td>65.0, 18.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>109.9–101.6</td>
<td>11.3–115.4</td>
<td>28.8–109.4</td>
<td>35.6–96.2</td>
<td>39.4–99.6</td>
</tr>
<tr>
<td>One year vs baseline cases vision loss</td>
<td></td>
<td>0.59</td>
<td>0.65</td>
<td>0.72</td>
<td>0.89</td>
</tr>
<tr>
<td>P</td>
<td>0.04</td>
<td>0.42</td>
<td>0.22</td>
<td>0.22</td>
<td>0.14</td>
</tr>
<tr>
<td>One year, no vision loss</td>
<td>83.9, 21.5</td>
<td>83.3, 19.2</td>
<td>93.3, 8.6</td>
<td>92.3, 8.9</td>
<td>91.8, 12.1</td>
</tr>
<tr>
<td>95% CI</td>
<td>68.8–99.0</td>
<td>67.6–99.0</td>
<td>88.1–98.4</td>
<td>87.0–97.7</td>
<td>84.6–99.1</td>
</tr>
<tr>
<td>One year, no vision loss vs baseline no vision loss</td>
<td></td>
<td>0.40</td>
<td>0.18</td>
<td>0.14</td>
<td>0.08</td>
</tr>
<tr>
<td>P</td>
<td>0.34</td>
<td>0.07</td>
<td>0.22</td>
<td>0.22</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline, all cases</td>
<td>71.4, 29.5</td>
<td>84.2, 27.6</td>
<td>82.4, 20.6</td>
<td>90.1, 19.7</td>
<td>76.7, 23.1</td>
</tr>
<tr>
<td>One year, all cases</td>
<td>75.3, 28.6</td>
<td>76.2, 28.8</td>
<td>86.0, 19.7</td>
<td>85.4, 19.9</td>
<td>84.8, 13.4</td>
</tr>
<tr>
<td>One year vs baseline, all cases P =</td>
<td>0.73</td>
<td>0.48</td>
<td>0.50</td>
<td>0.45</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Bold for correlation with P ≤ 0.05.*

**TABLE 3. Spearman rank correlation of baseline ADV categories**

<table>
<thead>
<tr>
<th></th>
<th>ND</th>
<th>DD</th>
<th>DV</th>
<th>NV</th>
<th>GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse eye acuity* correlation value</td>
<td>0.43</td>
<td>0.50</td>
<td>0.41</td>
<td>0.07</td>
<td>0.53</td>
</tr>
<tr>
<td>P</td>
<td>0.13</td>
<td>0.07</td>
<td>0.07</td>
<td>0.76</td>
<td>0.02</td>
</tr>
<tr>
<td>Worse eye contrast sensitivity* correlation value</td>
<td>0.13</td>
<td>0.53</td>
<td>0.14</td>
<td>0.23</td>
<td>0.19</td>
</tr>
<tr>
<td>P</td>
<td>0.67</td>
<td>0.06</td>
<td>0.58</td>
<td>0.34</td>
<td>0.44</td>
</tr>
<tr>
<td>Worse eye MD* correlation value</td>
<td>0.43</td>
<td>0.60</td>
<td>0.04</td>
<td>0.16</td>
<td>0.28</td>
</tr>
<tr>
<td>P</td>
<td>0.13</td>
<td>0.02</td>
<td>0.66</td>
<td>0.50</td>
<td>0.23</td>
</tr>
<tr>
<td>% worse eye central impairment* correlation value</td>
<td>-0.47</td>
<td>-0.54</td>
<td>-0.43</td>
<td>-0.09</td>
<td>-0.54</td>
</tr>
<tr>
<td>P</td>
<td>0.09</td>
<td>0.04</td>
<td>0.05</td>
<td>0.71</td>
<td>0.15</td>
</tr>
<tr>
<td>% binocular impairment* correlation value</td>
<td>-0.45</td>
<td>-0.62</td>
<td>-0.50</td>
<td>-0.19</td>
<td>-0.59</td>
</tr>
<tr>
<td>P</td>
<td>0.10</td>
<td>0.017</td>
<td>0.02</td>
<td>0.42</td>
<td>0.005</td>
</tr>
<tr>
<td>Better eye acuity* correlation value</td>
<td>0.24</td>
<td>0.07</td>
<td>0.62</td>
<td>0.23</td>
<td>0.41</td>
</tr>
<tr>
<td>P</td>
<td>0.42</td>
<td>0.81</td>
<td>0.064</td>
<td>0.33</td>
<td>0.07</td>
</tr>
<tr>
<td>Better eye MD* correlation value</td>
<td>0.47</td>
<td>0.28</td>
<td>0.37</td>
<td>0.35</td>
<td>0.26</td>
</tr>
<tr>
<td>P</td>
<td>0.09</td>
<td>0.34</td>
<td>0.10</td>
<td>0.14</td>
<td>0.12</td>
</tr>
<tr>
<td>Worse eye AGIS* correlation value</td>
<td>-0.44</td>
<td>-0.66</td>
<td>-0.19</td>
<td>0.49</td>
<td>-0.48</td>
</tr>
<tr>
<td>P</td>
<td>0.13</td>
<td>0.01</td>
<td>0.44</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Better eye AGIS* correlation value</td>
<td>-0.41</td>
<td>-0.40</td>
<td>-0.31</td>
<td>-0.42</td>
<td>-0.60</td>
</tr>
<tr>
<td>P</td>
<td>0.17</td>
<td>0.17</td>
<td>0.19</td>
<td>0.07</td>
<td>0.007</td>
</tr>
<tr>
<td>% binocular impairment at one year* correlation value</td>
<td>-0.36</td>
<td>-0.36</td>
<td>-0.58</td>
<td>-0.56</td>
<td>-0.52</td>
</tr>
<tr>
<td>P</td>
<td>0.15</td>
<td>0.20</td>
<td>0.008</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Bold for correlation with P ≤ 0.05.

* Baseline visual performance.
† One-year visual performance.
FIG. 1. The mean ADVS for all patients, patients with GCA visual loss, and patients without visual loss are expressed as a percent score along the x axis. At baseline, the day driving ($P = 0.04$) was significantly worse in patients with visual loss compared with patients without visual loss (remaining $P$ values range 0.22–0.46). At one year, the ADVS scores were lower, but not significantly, for patients with visual loss than for those without visual loss (range of $P$ values 0.07–0.34).

The AGIS score of the worse eye and the percent binocular impairment had the most significant correlations with the ADVS (Table 3). Night driving did not demonstrate significant correlation with any other visual parameter. Day driving demonstrated a moderate correlation with the worse eye mean deviation ($P = 0.60$), a moderate negative correlation with the percent of binocular impairment ($P = -0.62$) and the AGIS score of the worse eye ($P = -0.66$), and a modest negative correlation with the percent of central impairment in the worse eye ($P = -0.54$). The distance vision had a moderate correlation ($P = 0.62$) with better eye acuity. The

FIG. 2. The mean SF-36 scores for all patients, patients with GCA visual loss and patients without visual loss are expressed as a percent score along the x axis. At baseline, there was no significant difference between the mean category for patients with or without visual loss (range $P$ values 0.11–0.79). At one year, there was no significant difference for any category except the vitality score ($P = 0.02$) between all the patients at baseline and one year (range $P$ values 0.25–1.0). There was no significant difference for any category at one year between patients with or without visual loss (range $P$ values 0.08–0.92).
distance vision had a modest negative correlation with percent worse eye central impairment (\(P = -0.43\)) and percent binocular impairment (\(P = -0.50\)). The near visual (\(P = -0.49\)) had a modest negative correlation with the AGIS score of the worse eye. The glare score had a modest negative correlation with the worse eye acuity (\(P = 0.02\)), and a modest to moderated negative correlation with the percent binocular acuity impairment (\(P = 0.006\)), the worse eye AGIS score (\(P = 0.04\)), and the better eye AGIS score (\(P = 0.007\)).

The SF-36 scores for each category were not significantly different for patients with and without visual loss (Fig. 2). The SF-36 scores for the patient with bilateral visual loss were not worse than the scores from the other patients (data not shown). Mental health was the only category that correlated with any visual performance parameter (data shown only for percent binocular impairment. Table 4); there was a modest inverse correlation with the percent worse eye central impairment (\(r = -0.42\), \(P = 0.06\)) and percent binocular impairment (\(r = -0.43\), \(P = 0.06\)). The number of GCA symptoms (Table 4) only correlated modestly with the score of two SF-36 categories; there was a modest inverse correlation with the percent binocular acuity impairment (\(P = 0.06\)) and percent binocular impairment (\(P = -0.42\), \(P = 0.06\)).

One-year vision

In general, the visual dysfunction in the worse eye of patients with GCA caused visual loss at baseline persisted at one year (Table 5). No patients had new GCA visual loss after the baseline testing. For all patients, the mean deviation in the worse eye was better at one year (mean –3.6, SD 7.2, \(P = 0.002\)) than at baseline (mean –10.5, SD 9.5). Although the trend was for patients with visual loss to have better MD at one year (mean –9.3, SD 11.9) than at baseline (mean –24.4, SD 9.4), the improvement was not significant (\(P = 0.08\)). The visual acuity, contrast sensitivity, mean deviation, and AGIS score in the worse or better eye, the percent of binocular impairment were not significantly different from baseline. The visual acuity, contrast sensitivity, the AGIS score, and the mean deviation in the worse eye: and the percent binocular impairment remained significantly worse in patients with GCA induced visual loss.

One-year quality of life measures and correlations

At one year 14 patients had no symptoms of active GCA or polymyalgia rheumatica. Four patients without visual loss had one symptom, steroid responsive polymyalgia rheumatica (Tables 2 and 3, Figs. 1 and 2). Two patients with visual loss had symptoms, one with steroid responsive polymyalgia rheumatica and one with ischemia of the upper extremities that was also controlled with steroids. Three patients required oral hypoglycemic agents to lower elevated blood glucose and six others had elevation in blood glucose requiring no medication. No patient developed new systemic hypertension. At one year there were two vertebral fractures and no hip fractures.

---

**TABLE 4. Spearman correlation of SF-36 category scores**

<table>
<thead>
<tr>
<th>(r^*) number systemic symptoms</th>
<th>PF</th>
<th>RP</th>
<th>RE</th>
<th>SF</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>MH</th>
<th>(P = )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.17</td>
<td>0.26</td>
<td>0.42</td>
<td>0.31</td>
<td>-0.43</td>
<td>-0.08</td>
<td>0.06</td>
<td>-0.03</td>
<td></td>
</tr>
<tr>
<td>(r^*) percent of central vision impairment of worse eye</td>
<td>0.09</td>
<td>0.20</td>
<td>0.16</td>
<td>0.21</td>
<td>-0.21</td>
<td>0.03</td>
<td>-0.69</td>
<td>-0.42</td>
<td></td>
</tr>
<tr>
<td>(P = )</td>
<td>0.70</td>
<td>0.39</td>
<td>0.51</td>
<td>0.37</td>
<td>0.37</td>
<td>0.91</td>
<td>0.91</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>(r^*) percent binocular impairment</td>
<td>0.08</td>
<td>0.16</td>
<td>0.11</td>
<td>0.16</td>
<td>0.15</td>
<td>-0.01</td>
<td>0.06</td>
<td>-0.43</td>
<td></td>
</tr>
<tr>
<td>(P = )</td>
<td>0.73</td>
<td>0.49</td>
<td>0.64</td>
<td>0.49</td>
<td>0.53</td>
<td>0.95</td>
<td>0.78</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>(r^*) cumulative steroid dose</td>
<td>-0.36</td>
<td>-0.18</td>
<td>-0.22</td>
<td>-0.13</td>
<td>-0.10</td>
<td>0.07</td>
<td>0.32</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>(P = )</td>
<td>0.12</td>
<td>0.44</td>
<td>0.34</td>
<td>0.38</td>
<td>-0.66</td>
<td>0.76</td>
<td>0.16</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

* Baseline correlation values (Worse eye visual acuity, worse eye contrast sensitivity, worse eye MD not shown since no \(r\) value showed a trend or significant \(P\) value)

**TABLE 5. One-year visual performance**

<table>
<thead>
<tr>
<th>Patients with no visual loss, mean</th>
<th>Worse eye visual acuity</th>
<th>Better eye visual acuity</th>
<th>Worse eye contrast, log units</th>
<th>Better eye contrast, log units</th>
<th>Worse eye MD db</th>
<th>Better eye MD db</th>
<th>Binocular impairment, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with no visual loss, mean</td>
<td>0.43</td>
<td>1.09</td>
<td>1.14</td>
<td>1.56</td>
<td>-3.87</td>
<td>-1.65</td>
<td>5.2</td>
</tr>
<tr>
<td>Patients with visual loss, mean</td>
<td>0.29</td>
<td>0.26</td>
<td>0.52</td>
<td>0.26</td>
<td>4.24</td>
<td>3.64</td>
<td>7.6</td>
</tr>
<tr>
<td>Patients with visual loss, mean</td>
<td>0.34</td>
<td>1.66*</td>
<td>0.45</td>
<td>1.43*</td>
<td>-24.55</td>
<td>-8.55*</td>
<td>18.8</td>
</tr>
<tr>
<td>Patients with visual loss, mean</td>
<td>0.37</td>
<td>0.31</td>
<td>0.40</td>
<td>0.29</td>
<td>7.42</td>
<td>9.12</td>
<td>12.3</td>
</tr>
</tbody>
</table>

* Includes the results from the less affected eye in the case of bilateral GCA ischemia with the vision in this eye: visual acuity = 0.5, MD (mean deviation) = –30.1, and contrast sensitivity = 1.42 log units. and AGIS (Advanced Glaucoma Intervention Study) score of 20.
For all patients, those with vision loss and those without vision loss, the one-year ADVS scores were not significantly different from the baseline scores (Table 2, Fig. 1). Day driving was still worse in patients with vision loss than those without vision loss, but less significantly \( (P = 0.07) \). The trend for all the other ADVS categories was still worse in the patients with vision loss. The percent of binocular impairment had a significant moderate negative correlation with distance vision \( (r = -0.58) \), and near vision \( (r = -0.56) \), and a modest negative correlation with the glare score \( (r = -0.52) \) (Table 3).

At one year, the SF-36 scores were not significantly different from the baseline scores for all patients or patients with or without visual loss (Fig. 2). Patients with visual loss had SF-36 scores that were not significantly different from patients without visual loss. The Spearman analysis showed no correlation between the total steroid dose and any SF-36 category (Table 4) except the mental health score was modestly inversely correlated \( (r = -0.45, P = 0.05) \). The presence of hypertension, diabetes mellitus, or vertebral fracture did not correlate with any SF-36 category score (data not shown).

**DISCUSSION**

Patients with GCA caused visual loss had worse visual perception for all categories, but the difference from patients without visual loss was significant only for day driving. The sole patient with a global ADVS reduction was the only patient with bilateral GCA visual loss. In this small prospective study, when using nonparametric analysis, there were no strong correlations between the Activity of Daily Vision Scale categories and a variety of visual performance measures in patients with the systemic illness giant cell arteritis.

Although there was a modest to moderate correlation with scores in some ADVS categories and visual performance, not all visual parameters exhibited a consistent or significant Spearman correlation. The percent acuity impairment in the worse eye and the percent binocular impairment negatively affected the day driving and distance vision perception. The AGIS scoring of the worse eye and the percent binocular impairment each correlated with the most number of ADVS categories, three. Better visual acuity in the better eye of each patient was associated with improved distance vision perception. Our finding of modest to moderate, but not strong, correlations between the ADVS categories and visual performance has been reported in patients with visual loss from other causes (12,13).

At one year, the various measures of visual performance were unchanged from the baseline (point of entry into the study after four to five weeks of steroids) findings. The ADVS scores at one year were also similar to the baseline results. At one year, day driving and glare vision scores remained inversely correlated with the percent of binocular impairment (the greater impairment the worse the worse the patient’s perception). The day driving score no longer correlated.

The SF-36, a global quality of life instrument, baseline scores did not correlate with the presence or absence of visual loss or the number of systemic symptoms at baseline. Only the mental health score had any significant correlation with visual performance. There was a modest inverse correlation for the percent of binocular and worse eye central impairment. Except for a modest inverse correlation with the mental health score and total steroid dose, no SF-36 category score at one year correlated with the amount of steroids taken, the presence of visual loss, hypertension, diabetes mellitus, or vertebral fracture. Similar to results reported for patients with glaucoma (12), in general, patients with GCA, even those with visual loss, did not have the perception that their visual loss significantly impacted their general well-being. This was unexpected since GCA is a systemic disorder, which caused numerous symptoms in addition to loss of vision in our patients. Even the one patient with bilateral visual loss did not seem to complain of general health problems. Similar to other studies (22), we found that mental distress was the SF-36 category, which was worse in patients with vision loss at baseline.

In this study with a small sample size, we found that in an elderly population with a general systemic and visual disorder, the ADVS scale but not the SF-36 appeared to distinguish between those patients with and without visual loss. In the patient with bilateral visual loss, the ADVS reflected the dysfunction but the SF-36 still failed to be profoundly affected.

**Acknowledgment:** Paul Lee MD provided the ADVS scale and guidance used in analyzing data. Douglas Gaasterland, MD provided the computer software and manual to perform the AGIS analysis of the visual fields.

**REFERENCES**

Original Contribution

**Pneumocystis carinii** Granuloma of the Optic Nerve
A Histopathologic Case Report

David L. Knox, MD, and Wm. Richard Green, MD

A 30-year-old man under treatment for acute leukemia died of *Candida* sepsis and *Pneumocystis carinii* pneumonia. A small granuloma containing *Pneumocystis carinii* was found in one optic nerve.

**Key Words:** *Pneumocystis carinii*—Optic nerve—Granuloma.

**CASE REPORT**

A 30-year-old white man with acute lymphocytic leukemia was treated with systemic and local central nervous system chemotherapy by an Ommaya reservoir. His terminal illness featured disseminated *Candida tropicalis* infection in his liver and spleen as well as *Pneumocystis carinii* pneumonia.

**FIG. 1.** Left optic nerve, with a 0.5-mm area of inflammation and necrosis (arrowhead). Hematoxylin and eosin stain, × 25.

**FIG. 2.** Left optic nerve, detail of area of inflammation shown in Figure 1. Granuloma, with loss of myelin and axons, chronic inflammatory cells and central area of microorganisms. Hematoxylin and eosin stain, × 160.

Gross and microscopic examination of both eyes was unremarkable, except for a 0.5-mm lesion of the left optic nerve, which contained macrophages and a 0.1 central area of microorganisms that measured 7 to 8 µm in diameter and had slightly refractile walls (Figs. 1–3).

**DISCUSSION**

*Pneumocystis carinii*, an organism of low virulence, is found in the lungs of humans and a variety of animals (1). The organism has been classified as a protozoan because of its morphologic features, failure to grow on fungal media, and susceptibility to antiprotozoan drugs. Molecular genetic studies, suggest that *P. carinii* is more closely related to fungi (2).

Serologic testing in the first years of life has revealed that many healthy children develop antibodies as evidence of asymptomatic infection (3,4). Microorganisms remain dormant until immune deficiency caused by genetic dysfunction, cancer, or immunosuppression from AIDS, or chemotherapy for leukemia or lymphoma allow proliferation in lungs and spread into other organs.
Ocular involvement by *P. carinii* has been documented clinically and histopathologically, most commonly in choroid (5) and occasionally in conjunctiva, retina, and orbit (6).

We report the apparent first case of optic nerve involvement by *P. carinii*. Because there are no clinical details documenting visual acuity or field defect in this patient, we can only speculate that such a lesion would have caused a small peripheral field defect. In a terminally ill patient, it is unlikely that either the patient or his physicians would have noticed such a field defect.

Optic nerve should be added to the list of sites of involvement by *P. carinii* infection and considered as a possible mechanism for an acquired small field defect in an immunodeficient patient.

REFERENCES

Cotton-wool spots are the clinical manifestation of focal infarcts of the retinal nerve fiber layer. They rarely cause significant visual field loss. A large idiopathic cotton-wool spot in a 34-year-old healthy woman caused a nerve fiber bundle visual field defect and an afferent pupillary defect that remained after the cotton-wool spot had disappeared and the retina and optic nerve appeared normal.

Key Words: Cotton-wool spots—Visual field defect—Scotoma—Afferent pupillary defect.

A 34-year-old healthy woman presented with a 2-day history of an acute, painless, inferior field defect in the right eye. Her medical history was remarkable only for a tick bite 1 year earlier, for which she received prophylactic antibiotics.

Visual acuity was 20/20 OU with correction. There was a +1 afferent pupillary defect OD. Hardy-Rand-Rittler color plate testing was 19/20 OU. There was no ocular inflammation, and the intraocular pressure was within normal limits. Dilated fundus examination revealed a 1 disk-diameter cotton-wool spot superotemporally adjacent to the right optic nerve (Fig. 1). There were flecks of blood along the temporal rim of the cotton-wool spot. There was no swelling of the optic nerve or evidence of retinal vasculitis or vitreous cells. The left eye was normal. Fluorescein angiography confirmed the clinical findings of a large cotton-wool spot. Focal hypofluorescence was seen in the region of retinal swelling owing to blockage of the dye (not shown). There was late staining of the optic nerve but no dye leakage.

The complete blood count was normal (6.1 white blood cells, 12.2 hemoglobin, 36.3 hematocrit, 330,000 platelets, and normal differential). The erythrocyte sedimentation rate was elevated at 55. Serology testing was negative for Borrelia burgdorferi and Treponema pallidum IgG and IgM. Antinuclear antibody and rheumatoid factor tests were negative. Cerebral magnetic resonance imaging and magnetic resonance angiography studies were normal. Blood pressure and medical workup were normal. No diagnosis was reached.

Visual field testing 5 months later (Fig. 2) demonstrated a dense inferonasal nerve fiber bundle visual field defect corresponding to the location of the prior cotton-wool spot. Fundus examination now showed only slight nerve fiber layer fibrosis in the region of the prior cotton-wool spot (Fig. 3). There was no optic disk pallor or excavation.
Cotton-wool spots are transient, white, feathery-appearing opacifications, and swellings of the retina resulting from microinfarcts of retinal nerve fiber layer. They are frequently a manifestation of systemic arteriolar disease, most commonly diabetes, hypertension, and collagen vascular disease, but also seen in human immunodeficiency virus and other infections, hematologic disease and coagulopathies, pancreatitis, embolic disease, trauma, pregnancy, and idiopathic conditions (1). As many as 95% of patients with cotton-wool spots are identified as having a predisposing systemic condition (2). Histopathologic analysis demonstrates retinal infarction from focal arteriolar occlusion. Ischemic injury to the retinal ganglion cells results in disruption of normal axoplasmic flow and the accumulation of cellular mitochondria and debris in axonal swellings.

Our patient presented with a giant cotton-wool spot of idiopathic origin immediately adjacent to the optic nerve. This juxtapapillary location is an anatomic region through which most of the retinal ganglion cell axons from the temporal and superior retina pass to exit the eye. It damaged a significant number of ganglion cell fibers from the superotemporal retina, causing a large visual field defect and an afferent pupillary defect in the eye.

The infarct apparently did not involve the optic nerve because the disk itself was not swollen. Interestingly, no disk pallor or pathologic cupping resulted from the loss of nerve fiber bundles even 5 months after presentation.

Despite the large visual field defect and the APD, the retina appeared normal apart from mild, barely discernible fibrosis in the nerve fiber layer.

It has been axiomatic that visual fields are normal after retinal infarcts manifested by cotton-wool spots. However, nonspecific scotomas and nerve fiber bundle defects have been rarely described (3,4). This case serves as a reminder that a previous (and now vanished) cotton-wool spot could be the cause of a nerve fiber bundle defect, an afferent pupillary defect, and a normal-appearing fundus and optic nerve.

REFERENCES
Evolving Concepts in the Pathogenesis of Multiple Sclerosis and
Their Therapeutic Implications

Richard A. Rudick, MD

Recent evidence suggests that multiple sclerosis (MS) is a continuously active neuropathologic process, even during the subclinical relapsing/remitting phase of the disease. Patients commonly feel well and function without disability for many years, experiencing only occasional relapses and nondisabling symptoms. In time, many evolve into a pattern of continuously progressive neurologic disability termed secondary progressive MS (SP-MS). SP-MS is hypothesized to occur once disease severity has exceeded a threshold. Above that threshold, compensatory mechanisms are inadequate to maintain normal function, and further disease progression is accompanied by progressively worsening disability. Inflammation dominates the early stage of disease. Progressive axonal pathology may underlie clinical disease progression in later stages. These concepts have important implications related to the diagnosis, methods for patient follow-up, type and timing of disease therapy, and the testing of neuroprotective drugs in MS.

In recent years, concepts of multiple sclerosis (MS) pathogenesis have evolved rapidly. There is increasing recognition that, although the disease is largely subclinical in its early stages, the pathologic process is continuously active. Axonal and neuronal pathology may be accumulating during this period. Patients enter the secondary progressive MS (SP-MS) stage relatively late in the course of the disease, possibly because the extent of axonal pathology, has exceeded a threshold.

**RELAPSING/REMITTING MS AS A CONTINUOUSLY ACTIVE DISEASE**

Traditionally, patients with relapsing/remitting MS (RR-MS) have been viewed as having a relatively benign form of the disease, probably because of minimal disability between relapses. In many instances, patients have been reassured and observed without treatment. Multiple lines of evidence have converged to indicate that the pathologic process is active in RR-MS patients, however, and data demonstrate that irreversible tissue injury can accumulate without clinical symptoms during this phase. The pathologic process leads eventually to SP-MS in most patients. During RR-MS, the following features are noted:

1. **Areas of signal enhancement on magnetic resonance imaging (MRI):** Gadolinium-enhancing lesions occur in approximately 50% of patients with RR-MS on random MRI scans. These lesions occur with approximately 10 times the frequency of clinical relapses.

2. Newer imaging techniques demonstrate accumulation of imaging abnormalities. Magnetic resonance spectroscopy (MRS), magnetization transfer imaging (MTI), and high field strength MRI show an increase in abnormalities in the white matter that appears normal on conventional MRI sequences.

3. Pathology studies demonstrate transected axons in active MS lesions. Axonal transection corresponds to sites of active tissue inflammation, regardless of the disease duration.

4. **MRS shows neuronal pathology.** Neuronal markers are decreased in MS lesions and in normal-appearing white matter during the relapsing remitting phase of the disease.

5. **MRI shows progressive tissue loss.** Early in the disease, increasing brain atrophy can be measured.

**Areas of signal enhancement on MRI**

Approximately 50% to 70% of RR-MS patients have one or more gadolinium-enhancing lesions on a random cranial MRI scan (1,2). Each new gadolinium-enhancing brain lesion resolves after 4 to 6 weeks, leaving a residual T2 lesion, so that the volume of T2 brain lesions increases by approximately 10% per year in RR-MS pa-
tient groups. Clinical correlation studies have found that most gadolinium-enhancing brain lesions in patients with RR-MS are asymptomatic (3), and patients have been observed to have frequent new gadolinium-enhancing lesions with no clinical symptoms whatsoever. This has led to the concept that there is an active pathologic process as measured by MRI in RR-MS but that individual new lesions result in symptoms only when the lesion happens to affect an articulate part of the central nervous system (CNS), such as the optic nerve or spinal cord.

Subclinical MRI disease activity, as reflected by gadolinium enhancement, suggests brain inflammation. MRI pathology correlation studies have documented acute inflammation at the sites of gadolinium enhancement in MS tissue (4), and the presence of gadolinium-enhancing lesions correlates with cerebrospinal fluid (CSF) pleocytosis (5). Patients with RR-MS with increased CSF cell counts were found to be significantly more likely to exhibit clinical and MRI disease activity during 1 and 2 years of prospective follow-up (5). These data are consistent with the interpretation that gadolinium-enhancing lesions are a marker for active brain inflammation and, as such, a marker for subsequent MRI and clinical disease activity. In support of this, gadolinium-enhancing lesions on random cranial MRI scans are strongly associated with gadolinium-enhancing lesions on subsequent MRI scans, and with an increased volume of T2 lesions over the following years (6). The number of gadolinium-enhancing lesions on 6 monthly MRI scans was found to predict the relapse rate during a 12-month period (7). The relationship to progressive disability is unclear, but long-term follow-up studies are lacking.

Newer imaging techniques demonstrate accumulation of imaging abnormalities

MTI is an easily applied MRI technique that provides information on the structure of CNS tissue. Proton molecules associated with myelin are relatively nonmobile. As tissue water molecules become more mobile, magnetization transfer decreases. Therefore, this technique has been developed as a method to monitor myelin loss. MTI pathology correlation studies have documented acute inflammation at the sites of gadolinium enhancement in MS tissue (4), and the presence of gadolinium-enhancing lesions correlates with cerebrospinal fluid (CSF) pleocytosis (5). Patients with RR-MS with increased CSF cell counts were found to be significantly more likely to exhibit clinical and MRI disease activity during 1 and 2 years of prospective follow-up (5). These data are consistent with the interpretation that gadolinium-enhancing lesions are a marker for active brain inflammation and, as such, a marker for subsequent MRI and clinical disease activity. In support of this, gadolinium-enhancing lesions on random cranial MRI scans are strongly associated with gadolinium-enhancing lesions on subsequent MRI scans, and with an increased volume of T2 lesions over the following years (6). The number of gadolinium-enhancing lesions on 6 monthly MRI scans was found to predict the relapse rate during a 12-month period (7). The relationship to progressive disability is unclear, but long-term follow-up studies are lacking.

Pathology studies demonstrate transected axons in active MS lesions

Pathology studies have directly demonstrated that CNS axons are irreversibly damaged by the inflammatory process in active MS lesions. Trapp et al. (12) used confocal microscopy to demonstrate large numbers of transected axons topographically related to inflammation in active brain lesions from 12 patients with MS, confirming the findings from a separate histologic study of amyloid precursor protein in MS brain lesions (13). The data demonstrate that the inflammatory process destroys axons as well as myelin. The cumulative effect of this process might account for irreversible neurologic disability in the secondary progressive stage of the disease.

Results of animal experiments provide another cause of axonal injury in patients with MS. Animals devoid of myelin-associated glycoprotein (14) or proteolipid protein (15) created with gene knock-out technology were found to develop and function normally at first. But as the animals aged, they developed progressive neurologic deficits and Wallerian degeneration. This suggests that myelin provides a trophic function for CNS axons and that axonal pathology develops as a consequence of myelin disruption.

MRS shows neuronal pathology

In vivo MRS studies have demonstrated reduced levels of N-acetyl aspartate (NAA), a neuronal marker, in brain lesions and in normal-appearing white matter in patients with RR-MS, suggesting that axonal pathology is a consistent and early feature of the MS disease process (16–27). In one study, reduced NAA was observed in cerebral cortex adjacent to subcortical white matter lesions in eight children with MS (25). The average age of the children in that report was 15 years, and the average disease duration was 3.5 years. Recently, studies from a number of groups have shown reduced NAA in normal-appearing white matter. Interestingly, NAA falls most steeply in normal-appearing white matter during the RR-MS disease stage. The studies suggest that inflammation or related pathologic mechanisms result in axonal pathology during RR-MS, setting the stage for the secondary progressive stage of the disease.

MRI shows progressive tissue loss

Simon et al. (28) measured the diameter of the third and lateral ventricles, the area of the corpus callosum in the midsagittal plane, and the brain width in serial MRI scans in placebo-treated patients participating in the interferon beta (IFN-β)-1a (Avonex) clinical trial. After 1 and 2 years, there were significant increases in ventricular diameter and corresponding decreases in corpus callosum area and brain width. This was one of the first studies to indicate loss of brain tissue early in the course of MS. Enhancing lesions in the baseline scans were the strongest predictors of progressive third ventricular enlargement in these patients, suggesting that active inflammation promotes brain atrophy.

A normalized measure of whole brain atrophy, termed the brain parenchymal fraction (BPF), was also applied to patients in the INF-β-1a (Avonex) clinical trial (29). The BPF is derived from the cranial MRI by dividing the volume of brain parenchymal tissue by the total volume within the brain surface contour. It represents the proportion of volume within the brain surface that is tissue rather than CSF. As brain tissue is destroyed by the pathologic process, CSF spaces are secondarily increased, and BPF decreases. Placebo-treated patients in the Avonex clinical trial were found to have BPFs more than 5 standard deviations below the mean of the healthy control group. BPF decreased significantly during each
year of observation. More than 70% of the placebotreated patients had significant decreases in BPF during the 2-year observation. Importantly, decreasing BPF occurred in many patients without clinical relapses, and in many patients without worsening Expanded Disability Status Scale scores, implying the presence of a subclinical pathologic process resulting in brain tissue loss (see below).

WHAT CAUSES SP-MS?

In aggregate, the above findings support the hypothesis that MS is active in many patients early in the disease course and that clinical symptoms do not fully reflect its severity. Why do patients with RR-MS function reasonably well and appear stable between relapses? This may be because compensatory mechanisms are adequate to maintain neurologic function during RR-MS. Why do patients with SP-MS develop continued neurologic decline years after the disease onset? Perhaps because the extent of irreversible tissue injury has progressed beyond a threshold where compensatory mechanisms are inadequate to maintain neurologic function. The onset of progressive deterioration is typically delayed for 15 or more years after the onset of RR-MS. Intermittent clinical relapses during the RR-MS disease stage indicate the presence of the underlying disease process but do not accurately reflect its severity. This may be one of the reasons why the relapse frequency does not accurately predict the long-term prognosis. Once a critical threshold is exceeded, irreversible neurologic disability ensues. Beyond that point, any further disease progression results in progressive disability progression. This model implies that SP-MS represents a relatively late stage of the pathologic process that may be unrealistic at this stage of disease. It also implies the need for proactive monitoring and therapy during the RR-MS.

CLINICAL IMPLICATIONS OF MS AS A CONTINUOUSLY ACTIVE BRAIN DISEASE

When should therapy be initiated, and what is the optimal duration of therapy?

There is a growing consensus that disease-modifying therapy should be initiated early in the course of MS, before irreversible disability has occurred. The rationale for early therapy includes three concerns: 1) that the immunologic process leading to tissue injury becomes more complex as time passes and may be more difficult to control with immunosuppressive therapy (30,31); 2) that the inflammatory process is active in many patients with RR-MS during periods of clinical remission (1,3); and 3) that the inflammatory process results in irreversible axonal injury (12,32), which accumulates over time during the relapsing/remitting stage of MS. These considerations imply that disease-modifying therapy should be started when MS is definitively diagnosed because the patient is at risk for subsequent disability progression. Trials of INF-β-1a beginning with the first MS symptom have shown significant therapeutic benefit and long-term follow-up of these patients may clarify the importance of treating at the time of the first symptom.

Identifying patients at higher risk of progressive MS for early therapy is an alternative to treating all patients at the time of diagnosis. Unfortunately, clinical features are only weak predictors of subsequent disease severity, and their value for assigning prognosis to individual patients is limited. Disease severity measured by cranial MRI scan at the time of the first symptoms has been shown to predict MRI and clinical disease progression. This implies that patients with minimal disease by MRI scan could be evaluated with a follow-up MRI scan to determine the need for disease-modifying therapy. Identifying prognostic factors early in the course of MS is an important goal of future MS research.

The optimal duration of therapy has not been determined. For patients doing well, therapy should be continued because a study of INF-β showed increased disease activity when therapy was discontinued after 6 months (33). Studies are needed in which patients are randomly assigned to continue or stop therapy and then carefully followed under double-masked conditions.

What is the evidence that early therapy reduces the destructive pathology?

Recent evidence suggests that INF-β-1a inhibited progression of T1 hole volume in the Avonex study (34) and that INF-β-1b inhibited progression of T1 hole volume in the Betaferon SP-MS study (F. Barkhof, personal communication). Because T1 holes have been correlated with axonal loss in MRI pathology correlation studies (35), this suggests that the well-documented anti-inflammatory effect of INF-β could inhibit the destructive pathologic process. This possibility was directly supported by the finding that INF-β-1a (Avonex) reduced the rate of whole-brain atrophy in the second treatment year by 55% (29). It is reasonable to hypothesize that this beneficial effect on whole-brain atrophy would translate into meaningful clinical benefits. The duration of the effect, however, and the effect of other INF-β products or glatiramer acetate on whole-brain atrophy is currently unknown.

Two ongoing studies could provide empirical evidence for early treatment. Two forms of INF-β-1a (Rebif and Avonex) have been tested in separate studies for efficacy in patients with clinically isolated syndromes. In both studies, patients with clinically isolated syndromes were eligible for the studies if there were clinically silent T2 lesions. Avonex was shown to decrease the probability of converting to clinically definite MS by 50% and markedly reduced MRI disease progression (36). Rebif, in the dose tested, was also effective, but the results were more modest. In aggregate, the studies suggest that early therapy with INF-β can inhibit destructive brain pathology.

How should patients on monotherapy be followed up?

The poor relationship between clinical relapses and the severity of brain inflammation implies that more
accurate and sensitive markers of the pathologic process in RR-MS will be required to follow-up patients. Periodic cranial MRI scans may be useful in estimating MS disease activity and progression in some patients, to determine the need for disease-modifying therapy in patients with clinically benign disease, and to follow the response to disease-modifying therapy. Studies are needed to define precisely the methods and frequency for using MRI to monitor patients on disease-monitoring therapy. The number of gadolinium-enhancing lesions, the number of new T2 lesions, and normalized measures of whole brain atrophy show promise. Methods are urgently needed to incorporate standardized image acquisition and image analysis in the clinical setting.

What are the long-term benefits and risks of current MS drugs, and do the long-term benefits justify the cost of the drugs?

Long-term benefits of the current drugs can only be ascertained from existing studies because clinical trials run 2 to 5 years whereas MS unfolds over decades. Therefore, clinical trials provide information on only a limited part of the overall disease. Lengthy placebo-controlled studies are impractical because patients who are deteriorating withdraw from the study, leaving it less informative with time. Open-label studies do not provide definitive evidence about efficacy because patients who are doing well elect to remain on the drug, whereas patients who are deteriorating stop therapy to try something else. Thus results in observer bias favoring long-term efficacy, a problem called informative censoring. Despite their limitations, the studies suggest that available disease therapies are likely to have a beneficial effect on long-term disability. However, long-term cost-benefit analyses are needed.

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Contemporary Immunomodulatory Therapy for Multiple Sclerosis

Richard A. Rudick, MD

Multiple sclerosis (MS) is no longer considered an unmanageable disease. Five drugs have obtained regulatory approval to safely and effectively modify the course of MS. Three preparations of interferon β—Avonex (interferon β-1a), Betaseron (interferon β-1b), and Rebif (interferon β-1a)—have shown efficacy in relapsing-remitting MS and show promise in slowing the course of secondary progressive MS. Glatiramer acetate (Copaxone) has demonstrated efficacy in relapsing-remitting MS, and is being tested for the management of primary progressive disease. Mitoxantrone (Novantrone) has been approved for secondary progressive and progressive relapsing MS. There is a tendency toward early diagnosis and treatment based on the hypothesis that treatment effectiveness declines with advancing disease.

Several immunomodulatory drugs have become available for disease management in relapsing-remitting (RR) and secondary progressive (SP) multiple sclerosis (MS) during the past 7 years. There is a new emphasis on early therapy based on evidence that the disease process is continuously active, even during clinically quiescent phases of early MS, and that therapy will prevent irreversible tissue injury and diffuse axonal pathology.

AVAILABLE DRUGS FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS

Recombinant interferon β-1b (Betaseron [Berley Labs, Richmond, CA]), β-1a (Avonex [Biogen, Inc., Cambridge, MA]) and Rebif (Serono, S.A., Lausanne, Switzerland), and glatiramer acetate (Copaxone [Teva Marion, Partners, Kansas City, MO]) (Table 1) have been shown to be safe and effective in the management of RR-MS. Avonex and Rebif are recombinant interferon β preparations that are glycosylated and have amino acid sequences identical to natural human interferon β. Betaseron is produced by Escherichia coli and, unlike interferon β-1a, is nonglycosylated. The drug has a serine-for-cysteine substitution at the 17-amino acid position. Copaxone is a polymer of four basic amino acids that was originally synthesized as a mimic of myelin basic protein. These drugs were tested in separate multicenter, placebo-controlled, double-masked clinical trials (Table 2).

Betaseron was tested in 372 patients given 250 µg (9 MIU), 50 µg (1.8 MIU), or placebo by subcutaneous injection every other day for up to 5 years (1). The primary outcome measure was relapse rate. Treatment with the higher interferon dose reduced the relapse rate by 33%, increased the proportion of relapse-free patients from 16% to 31%, and reduced by twofold the number of patients with moderate or severe relapses of MS. Beneficial effects were maintained for patients who elected to remain in the blinded trial for up to 5 years (5). A statistically nonsignificant trend suggested that patients in the 250-µg arm were less likely to experience worsening by at least one point from the baseline Expanded Disability Status Scale (EDSS) sustained for at least 3 months.

Avonex was tested in 301 patients given weekly intramuscular injections (6 MIU, 30 µg) or placebo for up to 2 years (2,6). The primary outcome measure was time to onset of sustained disability progression, defined as deterioration from baseline by at least one point on the EDSS persisting for at least 6 months. Treatment with Avonex resulted in a significantly lower probability of sustained disability progression, and significantly fewer interferon β-1a recipients became severely disabled, defined as 6-month sustained worsening at least to the EDSS 4.0 or EDSS 6.0 levels (7). Patients at EDSS 6.0 require assistance to walk, and at this EDSS score, SP-MS has evolved in most patients. This finding suggests that interferon β therapy can prevent or delay transition...
from RR-MS to SP-MS in some patients. Treatment with Avonex also reduced the relapse rate by 32% in the cohort of patients treated for 2 years, and by 18% in all patients regardless of the study period (2).

Rebif was tested in 56% patients given 44 μg, 22 μg, or placebo by subcutaneous injection three times weekly for 2 years (3). The primary outcome measure was relapse rate. Treatment with the lower dose reduced the relapse rate by 29%, and treatment with the higher dose reduced the relapse rate by 32% after 2 years. Treatment with Rebif increased the proportion of relapse-free patients from 16% to 27% (lower dose) and 32% (higher dose). Treatment with Rebif also reduced the number of severe relapses, steroid courses, and hospital admissions for MS. There were statistically significant benefits in terms of EDSS change between baseline and 2 years and in the time to 3-month sustained worsening.

Both interferon β-1b and β-1a had beneficial effects on the disease process measured by cranial magnetic resonance imaging (MRI) scans. Betaseron resulted in significantly fewer new or enlarging T2 lesions in 52 patients studied at one of the clinical sites with MRI scans every 6 weeks, and significantly less annual accumulation of T2 lesions in the entire study group (8). In a separate study, Betaseron reduced the frequency of gadolinium-enhanced brain lesions (9). In the phase III trial, Avonex significantly reduced gadolinium brain lesions after 1 and 2 years of treatment, and decreased the number of new and enlarging T2 lesions after 1 and 2 years (2,10). These studies indicate that interferon β inhibits new brain lesion formation. Rebif also has prominent beneficial effects on MRI parameters, and particularly enhancing lesions and new and enlarging T2 lesions.

The significance of the prominent effects of interferon β on enhancing MRI abnormalities remains uncertain because of the lack of a documented relation between these abnormalities and subsequent neurologic disability (14). This may be clarified as studies focus more on the effects of interferon β on destructive pathologic process, as measured by the volume of T1 holes or brain atrophy. Nevertheless, the prominent effect of interferon β preparations on enhancing lesions suggests that interferon β therapy reduces brain inflammation. This conclusion was supported by the Avonex study, which found significantly reduced cerebrospinal fluid pleocytosis among Avonex recipients after 2 years of therapy (15).

Two studies tested the efficacy of interferon β in patients experiencing a first clinical demyelinating episode and with MRI signal abnormalities, which have predicted a high likelihood of future MS-like neurologic events. These studies enrolled patients with optic neuritis, transverse myelitis, or brainstem syndromes who had at least two periventricular T2 lesions. Avonex decreased the probability of conversion to clinically definite MS by 50%, and markedly reduced MRI disease progression (16). Rebif was also effective at the dose used, but the results were more modest.

All three interferon β preparations cause transient flu-like symptoms. Headache, myalgia, fever, or malaise, commonly last 24 to 48 hours after each injection, but the severity of these symptoms typically lessen after 6 to 12 weeks of therapy. Betaseron causes redness and swelling at the injection site and skin necrosis in 5% of the patients.

In the phase III clinical trials, neutralizing antibodies to interferon β were observed in 38% of Betaseron recipients (13), 22% of Avonex recipients (2), 23.8% of low-dose Rebif recipients, and 12.5% of high-dose Rebif recipients (3). The presence of neutralizing activity in the Betaseron study was associated with reduced clinical and MRI efficacy. In an open-label study, a single biologic assay was used to determine titers of neutralizing antibodies in patients treated clinically with Betaseron or Avonex (12). After 12 to 18 months of treatment, neutralizing antibodies were observed in 35% of patients treated with Betaseron, and in 7% of patients treated with Avonex. This finding raises the likelihood that interferon β-1b is more immunogenic than interferon β-1a. In a
TABLE 3. Features of pivotal trials in relapsing-remitting MS

<table>
<thead>
<tr>
<th>Primary result</th>
<th>Phase III study</th>
<th>Phase III study</th>
<th>Phase III study</th>
<th>Open label study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>Placebo 145</td>
<td>Placebo 187</td>
<td>Placebo 123</td>
<td>Placebo 126</td>
</tr>
<tr>
<td></td>
<td>RX 158</td>
<td>RX, 6 MIU 189</td>
<td>RX, 1.6 MIU 125</td>
<td>RX 125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RX, 12 MIU 184</td>
<td>RX, 8 MIU 124</td>
<td>0-5.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo 0-5.5</td>
</tr>
<tr>
<td>EDSS</td>
<td>1.0-5.5</td>
<td>0-5.0</td>
<td>1.0 (two in 2 yrs)</td>
<td>0-5.0</td>
</tr>
<tr>
<td>Min RR</td>
<td>0.67 (two in 3 yrs)</td>
<td>1.0 (two in 2 yrs)</td>
<td>1.0 (two in 2 yrs)</td>
<td>1.0 (two in 2 yrs)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>18-55</td>
<td>18-50</td>
<td>18-50</td>
<td>18-45</td>
</tr>
<tr>
<td>Dosage</td>
<td>30 µg</td>
<td>22 µg (6 MIU) SC TIW</td>
<td>50 µg SC daily</td>
<td>20 mg</td>
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<tr>
<td></td>
<td>IM weekly</td>
<td>44 µg (12 MIU) SC TIW</td>
<td>SC every other day</td>
<td>SC every day</td>
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<tr>
<td>Primary result</td>
<td>Sustained disability</td>
<td>Relapse count</td>
<td>Relapse rate</td>
<td>Relapse rate</td>
</tr>
<tr>
<td></td>
<td>(25% 0-6 MIU and 32% 4)</td>
<td>(25% 0-6 MIU and 32% 4)</td>
<td>(25% 0-6 MIU and 32% 4)</td>
<td>(25% 0-6 MIU and 32% 4)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Flulike symptoms</td>
<td>Flulike symptoms, skin</td>
<td>Flulike symptoms, skin</td>
<td>Mild skin reactions,</td>
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<td></td>
<td></td>
<td>reactions, decreased</td>
<td></td>
<td>sweating, palpitations</td>
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<tr>
<td></td>
<td></td>
<td>leukocyte count; increased transaminases</td>
<td></td>
<td></td>
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<tr>
<td>Prevalence of</td>
<td>Phase III study</td>
<td>Phase III study</td>
<td>Phase III study</td>
<td>Open label study</td>
</tr>
<tr>
<td>neutralizing</td>
<td>14% after 12 months;</td>
<td>38% of the patients were</td>
<td>35% NAB+ antibodies after</td>
<td>35% NAB+ antibodies after</td>
</tr>
<tr>
<td>antibodies</td>
<td>23% after 24 months,</td>
<td>NAB+ after 24 months.</td>
<td>12-18 months</td>
<td>12-18 months</td>
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<tr>
<td></td>
<td>two</td>
<td>Decreased clinical efficacy.</td>
<td></td>
<td>(12)</td>
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<td></td>
<td></td>
<td>(significance unknown);</td>
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<td></td>
<td></td>
<td>no methodology</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>to measure NAB to glatiramer acetate</td>
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</table>

EDSS, Expanded Disability Status Scale; IM, intramuscular; Min RR, minimal relapse rate to qualify for the study trial; MS, multiple sclerosis; NAB, neutralizing antibodies; RX, treated group; SC, subcutaneous.

Danish national study (17) of 754 patients starting treatment with interferon β, blood samples were collected at frequent intervals and analyzed using well-standardized assays in a central laboratory. Neutralizing antibodies varied in frequency from 7% to 42%. The frequency and titers of antibodies were considerably higher with interferon β1-b treatment than with interferon β1-a preparations. This finding may relate to immunological differences between interferon β1-b and β1-a. Additional variables that might be important are route and frequency of administration. The relative frequency of interferon β1-a products used as recommended is not known.

Because interferon β induces expression of many genes, the mechanisms of action in MS are likely complex (18). Putative mechanisms include: 1) inhibition of autoreactive T cells (19), 2) inhibition of major histocompatibility complex class II expression (20) with reduced antigen presentation within the central nervous system, 3) inhibition of metalloproteinases (21,22) or altered expression of cell-associated adhesion molecules leading to reduced cellular migration to the central nervous system (23), 4) induction of immunosuppressive cytokines (24) and inhibition of proinflammatory cytokines (25), leading to resolution of the inflammatory process.

Glatiramer acetate (Copaxone) is a polypeptide consisting of a random arrangement of four basic amino acids. The drug is thought to mimic myelin basic protein, and is postulated to induce myelin-specific suppressor T cells and to inhibit myelin-specific effector T cells. Copaxone was tested in 251 patients given daily subcutaneous injections (20 mg) or placebo for 2 years (4). The primary outcome measure was drug effect on the relapse rate. In the original 2-year study, Copaxone reduced the relapse rate by 29%. At the end of 2 years of therapy, patients were offered entry to an extension study, which was continued in a double-masked manner for approximately 1 additional year. The majority of patients continued in the extension study, and the beneficial effect on relapse rate was maintained (26). No significant effect was observed on sustained changes on EDSS, either in the original study or in the extension study. Although Copaxone was well tolerated, mild swelling and redness occurred at each injection site, and 15% of patients experienced brief episodes of flushing, chest tightness, palpitations, dyspnea, and anxiety.

MRI scans were not included as part of the Copaxone phase III study, but 27 patients underwent serial MRI scans at one site (27). There was a trend toward reduced gadolinium lesions favoring Copaxone, and a significant benefit in favor of Copaxone on a measure of brain volume loss (28). A similar trend in favor of Copaxone enhancing MRI lesions was found in a small study in 10 patients (29). A large study was recently completed to determine the effect of glatiramer acetate on MRI disease activity. Patients with RR-MS were required to have at least one enhancing lesion to enroll, and 239 of 485 patients screened were eligible to participate in the study. After a baseline MRI scan, patients were randomly assigned to glatiramer acetate or placebo, and followed in a double-blind protocol with monthly MRI scans for 9 months. During the 9-month double-blind
phase, there was a statistically significant 35% reduction in the total number of gadolinium-enhancing lesions in the glatiramer group compared with the placebo group (30). Interestingly, the therapeutic effect was first observed 3 to 4 months after treatment was initiated. This effect is considerably slower than the rapid-onset inhibitory effect of interferon β on enhancing brain lesions.

Direct comparisons across trials are not an accurate means of comparing drug efficacy because patient populations differ and outcome measures are subjective, poorly standardized, and used differently by different investigators. Nevertheless, Table 4 shows key outcomes from the pivotal trials of drugs for the management of RR-MS. The Table shows a similar treatment effect on relapse-rate reduction in RR-MS patients across studies. There is somewhat more between-study difference in sustained EDSS worsening, and it is unclear whether this represents a difference in treatment effect on MS-related disability or a difference in the way the EDSS measure was used. Nevertheless, considering all treatments together, the treatment effect on relapse rate appears to be roughly comparable with the treatment effect on sustained EDSS worsening. The effect of treatment on enhancing and T2 MRI lesions is greater than the effect on relapse rate, but the significance of this discrepancy is not yet clear.

### AVAILABLE DRUGS FOR SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

Interferon β-1b (Betaseron), β-1a (Rebif), and β-1a (Avonex) have been tested for efficacy in patients with SP-MS (Table 5). The European Study Group conducted a randomized, double-blind, placebo-controlled trial of subcutaneous Betaseron 8 MIU every other day versus placebo (31). Patients at 32 centers in 12 European countries were randomized to Betaseron (n = 360) or placebo (n = 314), or placebo (n = 308). Participants had confirmed SP-MS, with at least one documented relapse during the course of MS, entry EDSS between 3.0 and 6.5, and 1 EDSS-point progression, defined as sustained increase in EDSS score lasting at least 6 months. The study showed no difference between study arms on the primary study outcome, though significant benefits were observed in some of the secondary outcomes. Relapse rate was decreased by 43% (P < 0.01) in the 8-MIU arm, and by 29% (P < 0.05) in the 5-MIU/m2 arm. There was no significant difference between the doses on relapse rate. Change in T2 lesion volume between baseline and year 1 and 2, and T2 lesion volume at 2 years after study entry. The primary outcome measure was time to confirmed progression, defined as sustained increase in EDSS score lasting at least 6 months. The study showed no difference between study arms on the primary study outcome, though significant benefits were observed in some of the secondary outcomes. Relapse rate was decreased by 43% (P < 0.01) in the 8-MIU arm, and by 29% (P < 0.05) in the 5-MIU/m2 arm. There was no significant difference between the doses on relapse rate. Change in T2 lesion volume from baseline was significantly decreased in both treatment arms (P < 0.001), and again there was no dose effect. Newly enhancing lesions were reduced by 64% in the 8-MIU arm and by 76% in the 5-MIU/m2 arm. Although both reductions were statistically significant, there were no significant dose effects.

Another study of interferon β-1b enrolled 939 patients in 35 centers in the United States and Canada. Patients were randomized to receive subcutaneous Betaseron 8 MIU every other day (n = 317), 5 MIU/m2 (n = 314), or placebo (n = 308). Participants had confirmed SP-MS with at least one documented relapse during the course of MS, entry EDSS between 3.0 and 6.5, and 1 EDSS-point progression in the 2 years before study entry. The primary outcome measure was time to confirmed progression, defined as sustained increase in EDSS score lasting at least 6 months. The study showed no difference between study arms on the primary study outcome, though significant benefits were observed in some of the secondary outcomes. Relapse rate was decreased by 43% (P < 0.01) in the 8-MIU arm, and by 29% (P < 0.05) in the 5-MIU/m2 arm. There was no significant difference between the doses on relapse rate. Change in T2 lesion volume from baseline was significantly decreased in both treatment arms (P < 0.001), and again there was no dose effect. Newly enhancing lesions were reduced by 64% in the 8-MIU arm and by 76% in the 5-MIU/m2 arm. Although both reductions were statistically significant, there were no significant dose effects.

In a randomized European controlled trial of interferon β-1a (Rebif) (31), 618 patients with confirmed...
SP-MS were randomized to receive 22 μg Rebif subcutaneously three times per week (n = 209), 44 μg three times per week (n = 204), or placebo (n = 205). Patients had an EDSS between 3.0 and 6.5, and had worsened by at least one EDSS point during the previous 2 years. The primary outcome was time to confirmed progression in disability, defined as EDSS worsening for at least 3 months of 1 point for patients entering at 5.0 or below, or 0.5 points for patients entering at 5.5 or above. Time to sustained disability progression did not differ significantly between the study arms. As with the North American Betaseron study, there were significant benefits of treatment in a number of secondary endpoints. Both the low-dose and high-dose groups showed a 30% reduction in relapse rate (P < 0.01) and there was no dose effect. There were significant benefits in favor of either arm in number of steroid courses and hospital stays for relapses. There were also significant reductions in new and enlarging T2 lesions, enhancing lesions, and T2 lesion volume. The beneficial MRI effects were greater at the higher dose. A post-hoc analysis showed that women benefited more than men. In contrast to the European Betaseron study, the presence of prestudy relapses was associated with greater therapeutic effect during the clinical trial.

A recently completed randomized controlled trial of interferon β-1a (Avonex) for the management of SP-MS enrolled 436 patients with confirmed SP-MS to receive weekly intramuscular injections of 60 μg Avonex or placebo for 2 years. The primary outcome measure was 2-year change in the MS Functional Composite (MSFC), a new outcome measure for MS clinical trials (33-35). The MSFC consists of quantitative tests of arm function, walking speed, and cognitive function, expressed as a standardized score along a continuous scale. Avonex treatment was associated with a statistically significant benefit on MSFC z score change (median change from baseline, -0.10 for Avonex group vs. -0.16 in the placebo group, P = 0.033). There were also significant benefits on numerous other secondary outcome measures, including a 33% reduction in relapse frequency, reduced new or enlarging T2 lesions, enhancing MRI lesions, and significant benefits on 8 of 11 scales in the MS Quality of Life Inventory. Interestingly, there was no benefit observed on time to worsening on EDSS, or on EDSS change from baseline to 24 months. This may be better understood by analysis of the individual MSFC components. The overall benefit on the MSFC was driven by the upper-extremity score and the cognitive score. Consistent with the EDSS result, there was not a significant benefit of treatment on the ambulation score of the MSFC. This finding suggests that ambulation (which is the principal dimension captured by EDSS at this range of disability) is not as favorably affected by progression as are the other dimensions of the disease. The Avonex SP-MS trial result may help explain discrepant findings in the other SP-MS interferon studies. It also suggests that the MSFC is a more sensitive and probably more informative disability-related outcome measure than the EDSS.

The results of interferon β trials in patients with SP-MS have thus been mixed. This is particularly striking with the two Betaseron studies, which appear superficially similar and use an identical interferon β product administered with the same dose schedule. The European study showed a highly significant, though modest, benefit on disability progression, whereas the North American Study showed no differences. This discrepancy has led to comparison between the two study populations. The North American population was significantly older at entry, had a longer disease duration, fewer relapses in the previous 2 years, greater change in EDSS in the 2 years before study entry, and fewer MRI enhancing lesions at study entry. These differences suggest that the North American population showed less inflammation and possibly more noninflammatory axonal degeneration. Although speculative, this analysis would conclude that interferon β therapy is most effective in the earlier inflammatory stage of MS, and increasingly less effective in later stages characterized by progressive disability.

Mitoxantrone (Novantrone (Immunex, Seattle, WA)), an anthracenedione derivative introduced in 1979 for the treatment of patients with cancer, was recently approved for SP and progressive relapsing MS at an intravenous dose of 12 mg/m² every 3 months to a maximum cumulative dose of 140 mg/m². Novantrone has cytotoxic and immunosuppressive effects and has been used for the management of acute myeloid leukemia and symptomatic hormone-resistant prostate cancer. Approval for MS management was based on results of a placebo-controlled, double-blind, randomized, multicenter trial.

**TABLE 6. Key findings from pivotal trials in secondary progressive MS**

<table>
<thead>
<tr>
<th></th>
<th>Annualized relapse rate</th>
<th>EDSS sustained worsening (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose/wk</td>
<td>Placebo</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>60 μg</td>
<td>0.30</td>
</tr>
<tr>
<td>IFNβ-1a (Betaseron)</td>
<td>122 μg</td>
<td>0.71</td>
</tr>
<tr>
<td>IFNβ-1b (Betaferon)</td>
<td>875 μg</td>
<td>0.64</td>
</tr>
<tr>
<td>IFNβ-1b (Betaferon)</td>
<td>875 μg</td>
<td>0.28</td>
</tr>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>1,050 μg</td>
<td>0.28</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>12 mg/m²</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Based on Kaplan-Meier analysis of patients studied for 3 years in Betaseron, Betaferon, and Rebif trials, or 2 years in Mitoxantrone or Avonex trials. Adapted from the original publications or abstracts.* Significant differences from placebo.
CONTEMPORARY IMMUNOMODULATORY THERAPY FOR MULTIPLE SCLEROSIS

three elements contribute to the specificity of the immune response, and also to the downstream events resulting from T-cell activation. The nature of costimulatory molecules may determine whether a T cell develops into a memory cell or becomes tolerant to that particular antigen. Considerable work in experimental autoimmune encephalomyelitis (EAE) has defined immunodominant epitopes of myelin basic protein and the therapeutic potential of altered peptides that fail to induce EAE and protect treated animals from active or passive EAE induction. One such "altered peptide ligand" is CGP77116, an altered peptide of Myelin basic protein 83-99.

In one study, patients with confirmed MS were randomized in a placebo-controlled, double-blind, phase II study (36). The study was discontinued by a safety monitoring committee because 9% of patients developed hypersensitivity reactions. There were no increases in clinical relapses or new enhancing lesions in any patient, and a secondary analysis suggested that the volume and number of enhancing lesions was reduced at the highest dose tested (5 mg). A second study of this altered peptide ligand also was discontinued early (37). In this study, three patients had relapses of MS, two of whom also had markedly increased reactivity to myelin basic protein. The study raised a concern about the risk of antigen therapy.

At the present time, the future of antigen-specific immunotherapy is uncertain for a number of reasons. There is significant variability in myelin recognition between patients (38-39), significant change in myelin recognition within patients over time (40), and inadequate information about reliable methodologies to induce protective rather than inflammatory T-cell responses.

Trafficking

Movement of cells across endothelial barriers and into tissues requires molecular interactions between selectins and their receptors, integrins on leukocytes and their immunoglobulin-family receptors on endothelial cells, chemokines and their receptors, and various enzymes such as metalloproteinases. Inhibition of leukocyte trafficking is an attractive therapeutic strategy. The future of chemokine-based therapy is bright, but has not yet emerged in the MS field. Inhibition of very-late antigen 4, an α4β1 integrin, has emerged as a potential therapeutic strategy in MS. A randomized, double-blind, placebo-controlled trial of Antegren (Elan Pharmaceuticals, Dublin Ireland), a humanized monoclonal antibody to very-late antigen 4, was conducted in 72 patients with active RR-MS or SP-MS (41). Each patient received two infusions of Antegren or placebo 4 weeks apart, and was followed up for 6 months with serial MRI and clinical assessments. The treated group exhibited significantly fewer new enhancing lesions than did the placebo group during the first 12 weeks of the study. There was no effect of treatment on relapses, but the study was not designed to look at a clinical outcome. Inhibition of leukocyte integrins, such as Antegren, represents an appealing therapeutic strategy, and further studies are ongoing.

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PROMISING NEW APPROACHES FOR IMMUNOMODULATORY THERAPY

Altered peptide ligands

Productive interaction between antigens and T cells necessitates a major histocompatibility complex class II molecule on the surface of an antigen-presenting cell, together with a cognate antigen and T-cell receptor. All molecules on the surface of an antigen-presenting cell, together with a cognate antigen and T-cell receptor. All
Costimulatory molecules

Two reagents targeting costimulatory molecules are in the planning stages. The first molecule that is being targeted is CD40 ligand (CD154), and the reagent is a humanized monoclonal anti-CD40L (IDEC Pharmaceuticals, San Diego CA; and Biogen Inc., Cambridge MA). The IDEC-produced molecule has been tested in a phase I dose-finding study, and will be tested in a phase II trial with gadolinium enhancement as the target. Biogen has planned a phase II trial of anti-CD40L in MS patients, but the trial has not started because of concerns about thrombotic complications of anti-CD40L that have arisen in other studies.

Another promising target of immunomodulatory therapy is CTLA4 immunoglobulin. This fusion protein binds CD28 and may make T cells tolerant. Bristol Myers Squibb and Repligen have plans to test CTLA4 immunoglobulin in RR-MS.

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The Controlled High Risk Avonex® Multiple Sclerosis Trial (CHAMPS STUDY)

Steven L. Galetta, MD

The Controlled High Risk Avonex® Multiple Sclerosis Study (CHAMPS) tested whether interferon beta 1a (Avonex®) treatment would benefit patients who had experienced a first acute demyelinating event involving the optic nerve, brainstem/cerebellum, or spinal cord, and who displayed MRI brain signal abnormalities that have previously predicted a high likelihood of future MS-like events. The study randomized 383 patients into an Avonex®-treated and a placebo-treated group; both groups received intravenous methylprednisolone 1 gm/d followed by prednisone 1 mg/kg for 11 days. The Avonex®-treated group demonstrated a 44% reduction in the 3-year cumulative probability of developing clinically definite multiple sclerosis (rate ratio 0.56, 95% confidence interval 0.38 to 0.8; \( P = 0.002 \)). At 18 months, treatment with Avonex® was associated with a significant reduction of new T2 lesions, gadolinium enhanced lesions and T2 lesion volume. Among placebo-treated patients, 82% had developed a new subclinical MRI signal abnormality by the eighteenth month after study entry. Treatment benefit was observed irrespective of the qualifying event. The findings of this study support the efficacy of Avonex® therapy in significantly reducing the 3-year likelihood of future neurologic events and worsening of the brain MRI in patients with a first acute CNS demyelinating event.

Key Words: Optic neuritis—Multiple sclerosis—Interferon beta 1-a.

Interferon beta 1-A (Avonex®) has demonstrated a beneficial effect in reducing disability and relapses in a group of patients with relapsing/remitting multiple sclerosis (8). The Optic Neuritis Trial (ONTT) has shown that patients with first-attack optic neuritis treated acutely with intravenous methylprednisolone have a reduced rate of developing future MS-like neurologic events within a two year follow-up period. (1,2) an effect most evident among patients with two or more white matter MRI signal abnormalities typical of MS. However, this beneficial effect proved to be short lived, as corticosteroid-treated and placebo-treated groups had a similar cumulative probability of developing multiple sclerosis by three years (3,4). Several other studies have demonstrated that patients with isolated acute demyelinating syndromes and brain MRI scans demonstrating multiple signal abnormalities are at high risk of developing clinically definite multiple sclerosis (CDMS) (5–7).

These findings provided the rationale to compare the effect of interferon beta 1-A (Avonex®) to placebo in a group of patients at high risk for the development of CDMS.

METHODS

The Controlled High Risk Avonex® Multiple Sclerosis Study (CHAMPS) was conducted at 50 centers across the United States and Canada (9). Patients ranged in age between 18 and 50 years and had an acute isolated demyelinating event involving the optic nerve, spinal cord or brainstem/cerebellum. Each patient had at least two clinically silent brain MRI signal abnormalities greater or equal to 3 mm in diameter, one of which was periventricular or ovoid. All patients received intravenous methylprednisolone 1 g per day for three days within 14 days of the onset of their neurologic symptoms. This was followed by an oral prednisone taper beginning with 1mg/kg for 11 days and ending with a 4-day oral taper (20mg, 10mg, 10mg, 10mg). Patients were randomized by the nature of their clinical events and number of T2 MRI signal abnormalities (2–4, 5–7, ≥8). Patients in the first group were treated with a once-weekly intramuscular injection of interferon beta 1-A (Avonex®), while those in the second group were treated with placebo. Interferon therapy was initiated during the prednisone taper. All patients took acetaminophen for a twenty-four hour period after injection to minimize interferon-induced side effects.
Compliance was monitored by review of patient diaries and counting of used vials. Each patient was examined by a “treating” and an “examining” neurologist. All physicians and patients were masked to treatment assignment. Patients were examined one month after treatment initiation and thereafter at six-month intervals. If a patient was not stable after the month one visit, a visit was scheduled at month two to document stability. The treating neurologist documented adverse events and new neurologic symptoms. The examining neurologist performed examinations without taking histories.

The primary outcome measure was the development of CDMS, defined by the appearance of new neurologic or ophthalmologic events or progressive neurologic deterioration. Events had to persist for at least forty-eight hours and be documented by neurologic examination. Progressive deterioration was defined as a 1.5-point or greater increase in the expanded disability status (EDSS) score relative to baseline. Patients were also considered to have reached the primary endpoint if neurologic worsening was observed at the month two visit. All outcomes were verified by a masked endpoint committee.

Serial brain MRI studies provided secondary outcome measures. T2-weighted and enhanced T1-weighted images were obtained according to a standard protocol at baseline (while the patient was taking oral prednisone) and at 6, 12, and 18 months after study entry for those still enrolled. MRIs were interpreted at a single reading center.

The study was scheduled to extend for three years, based on an estimated three-year rate of development of CDMS of 50% in the placebo-treated group. A treatment effect of at least 33% was anticipated, together with a 15% study withdrawal rate before the diagnosis of CDMS. The primary outcome was determined on an intent-to-treat analysis. All P values were two-tailed; Kaplan-Meier analysis was used to document treatment effect.

RESULTS

The study enrolled 383 patients between April 1996 and April 1998. There were 193 patients in the interferon beta 1-A group and 190 in the placebo group. Baseline characteristics were similar in the two groups (Table 1). The trial was terminated in March 2000 when a data monitoring committee determined that the primary outcome measure had been met with a P value of less than 0.029 (9). Despite a premature termination, all active patients remained enrolled for at least 22 months.

Clinical findings

The cumulative probability of developing clinically definite multiple sclerosis was significantly lower in patients receiving interferon beta 1-A than in those receiving placebo (rate ratio .56, P = <.002, percent confidence interval .38 to .81) (Fig. 1). At the end of three years, the cumulative probability of CDMS was 50% in the placebo-treated group and 35% in the interferon 1-A-treated group. The treatment effect was slightly stronger (adjusted rate ratio = .49, P = <.001, percent confidence interval .33 to .73) when adjusting for age, type of presenting event, T2 lesion volume and gadolinium-enhancing lesions. There was no difference in treatment among patients presenting with optic neuritis, brain stem/cerebellar, or spinal cord events (P = .49). The diagnosis of CDMS was established by the occurrence of a second demyelinating event in all but five patients. One interferon beta 1-A-treated patient and two placebo-treated patients had an increase of the EDSS score by greater than 1.5 without an acute exacerbation. One placebo patient and one interferon beta 1-A were still progressing at the month two visit.

Brain MRI findings

Interferon beta 1-A-treated patients showed a significant treatment benefit at all intervals in a variety of brain
TABLE 2. Comparison of T2 MRI signal abnormalities in Avonex-treated and Placebo-treated patient groups at 18 months after study entry

<table>
<thead>
<tr>
<th>Number of T2 MRI signal abnormalities</th>
<th>Avonex (%)</th>
<th>Placebo (%)</th>
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<tr>
<td>0</td>
<td>47</td>
<td>18</td>
</tr>
<tr>
<td>1–3</td>
<td>31</td>
<td>40</td>
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<tr>
<td>&gt;4</td>
<td>22</td>
<td>42</td>
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was discontinued by 19% of patients in the interferon-treated group, and by 15% in the placebo-treated group. The most common reason for discontinuation was "patient request". Over 90% of patients were at least 80% compliant with study medication.

Implications

The CHAMPS study has shown that interferon beta 1-A reduces the conversion to CDMS in high-risk patients by approximately 50% (9). Even more compelling is the MRI data. New but silent MRI signal abnormalities appeared within 18 months in 82% in the placebo-treated patients who remained active in the study (Table 2). This finding indicates that a large number of such high-risk patients have ongoing silent demyelination. A prior longitudinal study of acute isolated demyelinating events had shown that the volume of MRI signal abnormalities at baseline is correlated with the degree of neurologic disability ten years later (5,6).

The CHAMPS trial suggests that Avonex® therapy significantly reduces the two-year likelihood of future neurologic events and worsening of the brain MRI in patients with a first acute CNS demyelinating event. It provides no information about the effect of Avonex® treatment on short-term disability or any long-term data on its effect on clinical relapses.

Future study

Further analysis of the CHAMPS data is ongoing. Treatment and MRI differences among the subgroups will be examined. For instance, did the number of MRI lesions at baseline predict increased risk for the development of CDMS? The CHAMPIONS Study (Controlled High Risk Avonex® Multiple Sclerosis Prevention Surveillance) will study the long-term effects and the factors associated with the development of CDMS. It will end in May 2003 when the last enrolled patient in the CHAMPS Study reaches the fifth anniversary of study entry.

REFERENCES

Clinical Outcome Measures for Research in Multiple Sclerosis

Laura J. Balcer, MD, MSCE

The development of new and more sensitive clinical outcome measures for research in multiple sclerosis (MS) has been fueled by the development of effective therapies. As such, active-arm comparison studies that require more sensitive clinical outcome measures are now commonplace. The Kurtzke Expanded Disability Status Scale (EDSS), the most widely used measure of neurologic impairment in MS, is particularly designed for classifying patients with respect to disease severity but has been criticized for its noninterval scaling, emphasis on ambulation status, relatively reduced sensitivity in the mid and upper ranges of scores, and absence of adequate cognitive and visual components. In response to perceived difficulties with the EDSS, the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force has developed the Multiple Sclerosis Functional Composite (MSFC). The MSFC includes three components that yield objective and quantitative results: 1) the timed 25-ft walk, 2) the nine-hole peg test, and 3) the 3-second paced auditory serial addition test. This scale has the advantages of continuous scoring with a composite Z score, standardized protocols, and high degrees of reliability and validity. Candidate visual function outcome measures for the MSFC, including the low-contrast Sloan letter chart, are currently under investigation. In addition to measures of neurologic impairment, health-related quality of life (HRQOL) measures have gained increasing importance as clinical trial outcome measures. The MS Quality of Life Inventory, a disease-specific HRQOL measure, has been developed to capture self-reported neurologic dysfunction and the impact of MS upon activities of daily living. MS clinical trials of the future, particularly active-arm comparison studies, will require more sensitive clinical outcome measures such as the MSFC. Measures of visual function and HRQOL should also be incorporated to capture the broad scope of neurologic impairment and disability in MS populations.

Clinical outcome measures are critical to the assessment of disease status and progression for clinical trials and other research in multiple sclerosis (MS). The development of new and more sensitive clinical outcome measures for MS research has been necessitated not only by characteristics of the disease process (such as variability of disease course among patients), but also by the development of effective therapies for MS. As such, placebo-controlled trials in MS are becoming, for the most part, impractical, and active-arm comparison studies, which require more sensitive clinical outcome measures, are now commonplace. In addition, several important aspects of neurologic function in MS, particularly cognition and vision, have been recognized as undermeasured by traditional MS clinical outcome measures (1-7).

The most commonly used scales in MS trials measure impairment (objective clinical signs and symptoms), disability (personal limitations on activities of daily living imposed by the impairment), or health-related quality of life (HRQOL—an individual’s assessment of how a health problem and its treatment affect the ability to perform valued activities and roles) (1,7-11). HRQOL measures may be categorized as generic (instruments that are designed to measure all important aspects of HRQOL, not only those of a specific disease or condition), or specific (scales that focus on aspects of HRQOL that are specific to a disease, function, condition, or population of interest) (7-15). Disease-specific HRQOL measures are often used to supplement generic HRQOL instruments, or may include a generic scale as a core measure (7,8,13). Table 1 includes an abbreviated list of the most commonly encountered clinical outcome measures used in MS research and clinical trials, including follow-up studies from the Optic Neuritis Treatment Trial (16-46). Scales indicated by an asterisk in Table 1 are discussed in detail in this article.

KURTZKE EXPANDED DISABILITY STATUS SCALE

The Kurtzke Expanded Disability Status Scale (EDSS) is the most widely used measure of neurologic impairment in MS clinical trials (27,47,48). The EDSS was derived from the Disability Status Scale (DSS) originally introduced by Kurtzke in 1955 (26). The DSS was an...
the ability to walk certain distances and a dependence on ambulation status—primarily on the brain (motor) function. Scores above 4.0 are highly dependent on ambulation status (the patient’s ability to walk for minimal distances with or without unilateral, bilateral, or wheelchair assistance).

For ratings of 4.0 or lower, the EDSS score is based on ordinal (noncontinuous) scale consisting of 10 steps or disease stages, primarily based on the clinical neurologic examination and patient ambulation status. In 1961, a set of functional groups (analogous to the functional systems (FS) that are used in the current EDSS scoring system) was added to complement the DSS, including categories for pyramidal (motor), cerebellar, brainstem, sensory, bowel/bladder, visual, mental, and other functions (49). FS scores were then used to generate DSS scores from 0 to 4. Scores above 4 reflected more advanced disease and were dependent on ambulation status (the patient’s ability to walk for minimal distances with or without unilateral, bilateral, or wheelchair assistance).

The DSS thus formed the basis for the current EDSS. A training CD-ROM for EDSS administration and scoring protocol has been modified (28). This may greatly limit the capacity of the EDSS to detect treatment effects in MS clinical trials, particularly in active-arm comparison studies in which the differences between groups may be small yet clinically significant (1–7).

The EDSS is an ordinal or noncontinuous scale for which the quantitative distances between scores are not well defined. Therefore, summary statistics such as mean and standard deviation, as would be used for interval (continuous) scales, may not be entirely appropriate for the reporting of EDSS scores. Mean and standard deviation are used commonly in MS clinical trials and natural history studies, although median and range may represent more appropriate summary statistics. Despite the many potential criticisms of the EDSS, including its non-continuous scoring, emphasis on ambulation status, and potential difficulties with sensitivity and reliability, the EDSS remains the standard clinical measure of neurologic impairment used in all major natural history and treatment trials and remains a useful tool for classifying patients clinically with respect to disease severity (1–4, 27, 47, 48).

The EDSS is administered by neurologists as a standardized measure of neurologic impairment in the setting of clinical trials, natural historyobservational studies, and clinical practice. A standardized protocol, Neurostatus, was recently developed to reduce potential interrater variability in the EDSS administration and scoring (28). The Neurostatus scoring protocol has been modified slightly from Kurtzke’s EDSS with respect to scoring within the 6.0–6.5 range (28). These changes are based on distance walked with unilateral versus bilateral assistance. A training CD-ROM for EDSS administration and scoring accompanies the Neurostatus system.

### MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE MEASURE

In response to perceived difficulties with the EDSS, the Multiple Sclerosis Functional Composite (MSFC) has been recently developed by the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force (MS Task Force) (4–6). This new scale has three components that yield objective and quantitative results: 1) the timed 25-ft walk, 2) the nine-hole peg test (50), and 3) the 3-second paced auditory serial addition test (51). Unlike the EDSS, the MSFC may be feasibly administered by trained technicians or other nonphysician personnel. Testing time for the MSFC is brief (approximately 15 minutes), and the facilities required for testing are simple (quiet examination room with table/desk and hallway for timed 25-ft walk) (6, 52).

Currently in use as the primary outcome measure for neurologic impairment in a recently completed randomized trial of interferon beta-1a in secondary progressive MS (IMPACT Study), the MSFC also has several advantages from a psychometric standpoint, including multidimensional design (measures several aspects of MS impairment), continuous scoring (composite Z score),

<table>
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<tr>
<th>TABLE 1. Commonly used clinical outcome measures in MS research and clinical trials</th>
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<tr>
<td><strong>Impairment scales</strong></td>
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<tr>
<td>Kurtzke Expanded Disability Status Scale (EDSS) (26, 27)*</td>
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<tr>
<td>Functional Systems (used in conjunction with EDSS) (26, 27)*</td>
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<tr>
<td>Neurostatus (standardized protocol based on EDSS) (28)*</td>
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<tr>
<td>Multiple Sclerosis Functional Composite (4–6)*</td>
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<td>Ambulation Index (29)</td>
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<tr>
<td>Scripps Neurologic Rating Scale (30)</td>
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<tr>
<td>Disability scales</td>
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<tr>
<td>Kurtzke EDSS (26, 27)*</td>
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<tr>
<td>Incapacity Status Scale (31)</td>
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<td>Environmental Status Scale (31)</td>
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<tr>
<td>Functional Independence Measure (32)</td>
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<td><strong>Health-related quality of life scales</strong></td>
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<tr>
<td>Generic measures:</td>
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<tr>
<td>36-Item Short-Form Health Survey (MSQLI) (26–36)*</td>
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<tr>
<td>Nottingham Health Profile (38)</td>
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<tr>
<td>Disease-specific measures for MS</td>
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<tr>
<td>MSQOL (7, 39)*</td>
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<tr>
<td>MS Quality of Life-54 (7, 40)</td>
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<tr>
<td>Functional Assessment of MS (7, 41)</td>
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<tr>
<td>Vision-specific measures</td>
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<tr>
<td>51-item National Eye Institute Visual Function Questionnaire (22, 42–45)*</td>
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<tr>
<td>25-item National Eye Institute Visual Function Questionnaire (22, 44–46)*</td>
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<tr>
<td>Impact of Visual Impairment Scale (subscale in MSQLI) (7, 39)*</td>
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* Study discussed in detail in text.
standardized protocols, and high degrees of concurrent and predictive validity when compared with the EDSS and with surrogate markers for MS disease activity such as magnetic resonance imaging (4–6,52). In a study of participants in a phase III trial of interferon beta-1a for relapsing MS (52), MSFC scores correlated significantly with EDSS at baseline ($r_s = -0.42, P < 0.0001$) and at 2 years ($r_s = -0.68, P < 0.0001$). Baseline MSFC scores were also significantly predictive of magnetic resonance imaging brain parenchymal fraction (a measure of degree of brain atrophy/neuronal loss) at 2 years ($r_s = 0.52, P < 0.0001$).

A single continuous score for the MSFC (referred to as the composite Z score) is derived by combining Z scores for each of the three components (4–6). A Z score represents the number of standard deviation units that a patient’s score is above or below the average score from a standardized population (pooled MS population or clinical trial baseline data selected to represent the standard). Z scores, as used for the MSFC and its components, are continuous scores (mean and standard deviation may be appropriately used as summary statistics), are more sensitive to changes over time, and allow direct comparison of scores with standard MS or control populations (6). Administration of the MSFC by nonphysician personnel also permits more thorough masking of neurologists to patient outcome measure results during the course of MS clinical trials, thus reducing the potential for bias. Standardized protocols for administration of the MSFC have been developed by the MS Task Force (53).

VISUAL FUNCTION OUTCOME MEASURES FOR MS RESEARCH AND CLINICAL TRIALS

Visual impairment is a leading cause of symptoms in patients with MS (54–57). The quantitative assessment of visual function in MS clinical trials (the EDSS), however, has been generally limited to measures of Snellen visual acuity (58). As recognized by the MS Task Force, the MSFC, despite its many advantages, does not yet include an assessment of visual function (4–6). In the evaluation of candidate MSFC visual components, Snellen acuity did not change over time or demonstrate concurrent changes over time with EDSS scores (5). There are two potential reasons for this: 1) Snellen acuity may not be sufficiently sensitive in patients with MS and 2) the potential for visual acuity to influence overall EDSS scores may be limited (the visual function score may become “buried” within the overall score), particularly among patients who have difficulty with ambulation (59). The need for evaluation of new candidate visual measures for assessing clinical outcomes in patients with MS is clear.

Numerous investigations have indicated that measures of contrast sensitivity and contrast letter acuity may be the most sensitive measures of visual dysfunction in patients with MS, even among those with Snellen acuities of 20/20 or better (23,25,59–73). A new set of contrast letter acuity charts, the Low-Contrast Sloan Letter Charts (LCSLC), has demonstrated a high degree of intrarater reliability when used for testing in patients with MS and in disease-free controls of similar age (59). Contrast letter acuity testing using the LCSLC also captures aspects of visual and neurologic function in MS that are not captured by Snellen visual acuity or ambulation status (59). More recent studies have shown that LCSLC testing is both a valid and feasible measure of visual function among patients with relapsing/remitting and secondary progressive MS (74). In a cross-sectional study of 50 patients with MS at the University of Pennsylvania, rank correlations of LCSLC scores (1.25% contrast level) with MSFC and EDSS scores were significant yet modest to moderate in magnitude ($r_s = 0.49, P = 0.0006$ for LCSLC versus MSFC; $r_s = -0.37, P = 0.008$ for LCSLC versus EDSS), supporting a potential role for LCSLC as an MSFC visual component (74).

MEASURES OF DISEASE-SPECIFIC AND VISION-SPECIFIC HRQOL IN MS

MS may have important and lasting effects on HRQOL that are not entirely captured by measures of neurologic impairment (7,9,10,40,41,58,75,76). HRQOL refers to an individual’s assessment of how a health problem and its treatment affect the ability to perform valued activities and roles (7,11,12). HRQOL measures are unique in that they capture the patient’s perspective on the impact of illness or treatment. There is consensus among MS investigators that HRQOL measures should be incorporated into ongoing data collection regarding the effects of MS and its treatments (7,8). Generic measures of HRQOL, including the 36-item Short-Form Health Survey from the Medical Outcomes Study (SF-36) (33–36), have demonstrated the impact of MS on important aspects of functioning and well-being. Although they demonstrate construct validity in MS, generic scales may not capture the impact of specific symptoms (7,8,40,41). The use of vision-specific HRQOL measures, including the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) and the 25-item National Eye Institute Visual Functioning Questionnaire (VFQ-25), in patients with MS has been recently investigated among participants in the Optic Neuritis Treatment Trial (21,22,42–45).

Multiple Sclerosis Quality of Life Inventory

The Multiple Sclerosis Quality of Life Inventory (MSQLI) has been developed as a disease-specific HRQOL instrument to complement measures of neurologic impairment (the EDSS and MSFC) in patients with MS (7,39). The MSQLI is a health profile measure that consists of a core generic scale, the SF-36, and nine other scales that capture various symptoms and aspects of HRQOL that have been identified as important to patients with MS (7). Although the SF-36 captures major domains of general health, the nine symptom-specific subscales of the MSQLI capture fatigue, pain, sexual satisfaction, bladder function, bowel function, perceived visual function, perceived cognitive function, emotional status, and social functioning (Table 2) (7).
TABLE 2. VFQ-25 and MSQLI subscales and summary measures

<table>
<thead>
<tr>
<th>VFQ-25</th>
<th>MSQLI</th>
<th>MSQLI (symptom-specific scales)</th>
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<tr>
<td>Distance activities [3]</td>
<td></td>
<td>Bowel Control Scale [5]</td>
</tr>
<tr>
<td>Mental health [4]</td>
<td>Mental Health Inventory [18]</td>
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<tr>
<td>Role difficulties [2]</td>
<td>MOS Modified Social Support Survey [18]</td>
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Dependency [3], Driving [2], Color vision [1], Peripheral vision [1]

Composite score [24 items — unweighted average of all item scores excluding general health (45)]

Numbers of items are in brackets.
VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; MSQLI, Multiple Sclerosis Quality of Life Questionnaire; SF-36, 36-item short form health survey.

Fischer (7) recently reported high levels of reliability and evidence supporting content and construct validity for this measure in a large-scale field test. Several design features of the MSQLI have led to its use as a measure of disease-specific HRQOL measure, including multidimensional design (nine symptom-specific scales) and inclusion of an established generic core (the SF-36). The reliability and validity of the SF-36 have been established across a variety of conditions, and population norms from patients with a variety of conditions, including visual impairment, are available (33–36). Two summary scales for the SF-36, the Physical Component Summary and the Mental Component Summary, are included among the MSQLI subscales, as detailed in Table 2.

National Eye Institute Visual Functioning Questionnaires

Visual function and self-perceived visual impairment are important aspects of HRQOL in patients with MS (22,58). Accordingly, a five-item measure of self-perceived visual function, the Impact of Visual Impairment Scale, has been included as one of the nine symptom-specific subscales of the MSQLI (Table 2). Independent of the development of the MSQLI, the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) has been validated as a measure of vision-specific HRQOL (44,45). The VFQ-25, and the larger scale from which it was developed, the 51-item NEI-VFQ (42,43), are not specific to MS but have been used to demonstrate self-perceived visual impairment in patients with a variety of ocular disorders, including recovered optic neuritis, glaucoma, age-related macular degeneration, and many others. The VFQ-25 consists of 12 subscale scores and an overall composite score (45), as outlined in Table 2.

Signs and symptoms of visual impairment are strongly related to overall HRQOL, particularly among patients with MS and optic neuritis (58,77,78). In the Optic Neuritis Treatment Trial cohort, vision-specific HRQOL scales captured self-perceived visual dysfunction at 6 months and at 5 to 8 years after an attack of acute optic neuritis (21,22). In the latter study, the 51-item NEI-VFQ results were similar when items from the short-form version (VFQ-25) only were used for analysis (22). Self-perceived visual dysfunction in this study was more common among those patients from the Optic Neuritis Treatment Trial who had developed clinically definite MS. This relationship was observed even though neurologic impairment in these patients was generally mild (70% of the 134 patients with MS had EDSS scores ≤2.5, indicating minimal disability).

Self-reported Visual Dysfunction in MS

Studies among clinically heterogeneous cohorts of MS patients have provided evidence that the VFQ-25 captures aspects of visual dysfunction that are not entirely captured by visual acuity or ambulation status (46). Modest but significant correlations of VFQ-25 composite scores with binocular visual acuity (r = 0.33, P = 0.003) support construct validity for VFQ-25 scores in MS populations (the VFQ-25 is measuring some aspect of visual dysfunction in MS) (79). Additional items, with content more specific to MS and other neuro-ophthalmologic disorders (such as double vision), may enhance the capacity of the VFQ-25 to capture self-perceived visual dysfunction in patients with MS. Further examination of how measures of visual function may relate to vision- and disease-specific HRQOL in MS is needed to determine which visual function outcome measures best capture aspects of HRQOL most valued by patients.

CONCLUSION

Clinical outcome measures are crucial to the demonstration of disease progression and treatment efficacy in MS research. With the advent of active-arm comparison studies of MS therapies, the need for more sensitive and reliable yet practical measures of neurologic impairment has led to the development of the MSFC. Despite the multidimensional nature of the MSFC (it includes measures of arm, leg, and cognitive function), measures of visual function such as the LCSLC must undergo further investigation for potential inclusion. Given the increasing importance of assessing HRQOL as a factor in patient outcomes, measures such as the MSQLI and VFQ-25 are likely to be included in future MS clinical trials. Despite the advantages of the MSFC, the EDSS—the
REFERENCES


CLINICAL OUTCOME MEASURE FOR RESEARCH IN MS

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Optic Neuritis: Historical Aspects

Nicholas J. Volpe, MD

Optic nerve disorders were not reliably diagnosed until the late nineteenth century when ophthalmoscopy became part of the ophthalmic examination. By the early 1900's, all of the salient clinical features of optic neuritis and its relationship to "systemic sclerosis" were recognized, but there was much controversy and misunderstanding about its differential diagnosis, pathogenesis, and possible treatment. During the twentieth century, physicians began to distinguish optic neuritis from infectious, hereditary, toxic, nutritional, and ischemic optic neuropathies. The development of magnetic resonance imaging and the results from recent clinical trials have enhanced our understanding of the relationship between optic neuritis and multiple sclerosis. The next decade holds the promise of further elaborating the pathogenesis and treatment of optic neuritis.

Key Words: Optic neuritis—Retrobulbar optic neuritis—History—Multiple sclerosis—Optic nerve.

INTRODUCTION

Much of the clinical profile of optic neuritis had been established by the late 1800's. The invention of the ophthalmoscope by Helmholtz in 1845 allowed ophthalmologists to differentiate types of "amaurosis" and to localize vision loss to the optic nerve. By the 1880's, von Graefe (1) and Nettleship (2), had described many of the salient features of the clinical syndrome that we now call idiopathic optic neuritis. Several individuals were accumulating large series of patients by the turn of the century. In 1884, based on a series of 28 patients, Nettleship offered the following description of patients with optic neuritis:

"They are characterized by failure of sight limited to one eye, often accompanied by neuralgic pain about the temple and orbit and by pain in moving the eye; many recover but permanent damage and even total blindness may ensue; there is at first little, sometimes no, ophthalmoscopic change, but the disc often becomes more or less atrophic in a few weeks, and occasionally there are slight retinal changes." (2)

The subsequent literature abounds with discussions of infectious or toxic etiologies, and proposals of barbaric treatments often claimed to be successful because of the under-appreciated rate of spontaneous recovery. The distinction between optic disc swelling secondary to papilledema and other causes of optic disc swelling was reported in the early part of the twentieth century. The association of optic neuritis with multiple sclerosis was also established at that time. However, except for increasing clinical sophistication allowing better distinction of optic neuritis from other forms of disc swelling and optic neuropathy, very little further insight had been gained into this disorder until 15 years ago. Patients could be counseled in 1985 much the same way they could be counseled in 1885. (The text Optic Neuritis and Its Differential Diagnosis by Perkin and Rose (3) published in 1979 summarizes the available literature until that time.) It was not until 140 years after the invention of the ophthalmoscope, with the application of the randomized clinical trial, magnetic resonance imaging, and the science of immunomodulation to the study of optic neuritis, that we have been able to make dramatic strides into understanding the etiology, treatment, and prognosis of idiopathic optic neuritis.

OPTIC NEURITIS IN ANTIQUITY

Before the invention of the ophthalmoscope in 1845, diseases of the fundus were impossible to recognize. Ancient physicians divided all eye diseases into "ophthalmia" or "blindness". "Ophthalmia" included all varieties of conjunctival and corneal diseases recognized through inspection of the globe. "Blindness" referred to vision loss not based on an obvious change in the visible surface or media of the eye. Blindness was often considered a divine punishment for sin. Within that group, optic neuritis may have accounted for some of the "miraculous" spontaneous cures.
The earliest references to optic nerve dysfunction as a mechanism for vision loss are found in Arabic texts of ophthalmology written in the ninth century. In what is believed by some to be the first major textbook of ophthalmology, Hunain Ibn Is-Haq (4) described three different forms of paralysis of the eye: those involving perception alone, those involving eye motion alone, and those involving both (4). In these early descriptions, he does not distinguish optic neuritis from other diseases of the posterior segment. However, there are specific references in this volume (and others) to pain and heaviness, "swelling" of the optic nerve, and the afferent pupillary defect (4):

"Therefore we see that the vision has ceased or diminished without our finding any change in the pupil and there is a heaviness in the head and particularly its deep part and the parts surrounding the orbit. We know that the affection is caused by an abundant moisture which has run to the optic nerve of the eye and has compressed or swelled it ... the argument for the obstruction of the nerve is if you shut one eye [the unaffected eye] and observe whether the pupil of the other is dilated."

Another Arabic writer, Ali Ibn Isa, referred to inflammation of the optic nerve, although he may have been describing papilledema, as he related "the cause of the blindness to the ventricles of the brain." (5) In his textbook of ophthalmology, Isa describes various affections of the optic nerve, including those resulting from "warmth, cold, humidity etc".

**OPTIC NEURITIS IN THE PRE-OPTHALMOSCOPE ERA**

In one of the earliest English language textbooks of ophthalmology, published in 1823, George Frick (6) wrote that optic neuritis is:

"a species of blindness which is produced by some immediate affection of the optic nerve or its expansion into the retina ... it may take place suddenly or slowly and be transient, permanent or intermittent."

His description suggests that, without the advantage of the ophthalmoscope, it was impossible to distinguish uveitis, migraine, retinal detachment, optic nerve and orbital apex disorders. Frick makes reference to severe pain in the orbit preceding vision loss, abnormal responses of the pupil to light, and the visual behavior of patients with central scotomas:

"amaurosis from whatever cause ... is generally characterized by a very dilated pupil which is not affected by any degree of light which is made to fall upon the retina ... [the patient with amaurosis] is obliged to turn his head to render them [objects] distinct."

Manuals written by Saunders (7) in 1821 and Littell (8) in 1846 present a similarly confused impression of optic nerve and retinal diseases.

**OPTIC NEURITIS IN THE POST-OPTHALMOSCOPE ERA**

With the widespread use of the ophthalmoscope in the second half of the nineteenth century, the various diseases affecting the optic nerve and retina became distinguishable. Optic neuritis was first described with some uniformity by von Graefe in 1860 (1) and by Nettleship in 1884 (2). Nettleship acknowledged that Leber, Hutchinson, and Hock had previously described cases of optic neuritis. Nettleship points out confusion with tobacco amblyopia in Leber's writing and describes Hutchinson's series as having a variable group of patients and Hock as describing the characteristic pain of optic neuritis (which Nettleship attributed to "stretching of the inflamed optic nerve sheath.") Nettleship states that:

"Under this rather vague title I wish to refer to certain not very common cases in which acute inflammation seems to take place in some small part of the course of the optic nerve."

Although he identified all the salient features of optic neuritis, he did not mention a relationship to other relapsing and remitting neurologic symptoms. Nettleship commented on the failure of sight being noticed quickly and reaching its worst within two to three days. He reported that pain usually began shortly before vision loss and that it worsened with eye movements or pressure on the globe. Vision loss is vividly described:

"The defect in vision is often described at first as a 'gaze' or a 'yellow mist' or a 'dark patch' or a 'spot' which covered the object looked at and gives an unnatural color, the hand looking, for example, as if covered by a brown glove."

Eleven of his sixteen patients displayed a central scotoma, and three also demonstrated peripheral field constriction. He described patients with healthy appearing optic nerves and others where there were "decided, if slight, changes much earlier." He suggested that the cases with normal optic nerves might have had a perisstitis in the optic canal, but among those with disc swelling, he could not "suppose the mischief to be seated so far back". He noticed the most significant recovery to be complete within 4 to 6 weeks. Up to nine of his patients were thought to have syphilis, although he did not specifically implicate this infection as the cause of vision loss. He distinguished "neuritis" patients with optic nerve head swelling from those with increased intracranial pressure resulting from anterior cerebral lobe tumors (papilledema) by the presence in the latter of vomiting, convulsions, and other cerebral symptoms.

Parinaud (9), Uhthoff (10), Buzzard (11), and Gunn also contributed early descriptions of optic neuritis (12). Parinaud described dyschromatopsia. Uhthoff detailed the visual field defects, various patterns of optic disc pallor, and the transient blurring of vision occurring with exercise that has become to be known as "Uhthoff's symptom." Buzzard's 1893 paper summarizes these contributions and contains a detailed discussion of optic disc.

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pallor as part of multiple ("disseminated") sclerosis. Among 100 patients with disseminated sclerosis, he found 42 with optic disc pallor, and emphasized the importance of vision loss with disc pallor in distinguishing true from "hysterical" forms of disseminated sclerosis. Buzzard credits Charcot (13) with the first description of "amblyopia" as a frequent symptom of cerebrospinal disseminated sclerosis. Buzzard writes:

"Amblyopia and optic atrophy have long been recognized among the symptoms of disseminated sclerosis ... but the frequency has not been appreciated. Is this not due to the fact that a very large portion of cases of disseminated sclerosis are diagnosed as cases of hysteria? The visual field disorder, consisting as it so commonly does of a concentric limitation of the visual field has the effect of appearing to confirm this erroneous diagnosis. I can not help thinking that the visual troubles so often supposed to mark a case as one of hysteria are really very often dependent on an organic cause... Are not many of the cases of retrobulbar neuritis of the ophthalmologists really examples of the "hysterical" form of disseminated sclerosis." (11)

Buzzard distinguished between the disc pallor of disseminated sclerosis and that of tabs dorsalis. Tabs, he believed, had more severe and permanent vision loss and more marked disc pallor:

"... the look of what so often is encountered in tabes-flat, dense and uniform, of a cold bluish-grey tone, suggesting the idea of it being painted in an opaque oil colour, with a very few retinal vessels lying upon it, and a marked absence of any minute vascularity."

Based on his experience with approximately 350 cases of optic neuritis, Gunn (3,12,14,15) concluded that an infectious etiology was likely. He divided cases into isolated "acute retro-ocular neuritis" without disc pallor or other neurologic manifestations and those in which there were acute episodes of optic neuritis as well as disc pallor and other neurologic manifestations. He described the presence of visual loss as a feature that distinguished optic neuritis from conditions in which disc swelling was associated with intracranial disease such as tumor, wherein chronic disc swelling was associated with preserved visual function (12). He reasoned that central scotomas were common in optic neuritis because the "optico-macular fibers are the most active physiologically in function and therefore will undergo most rapidly the normal degenerative changes." He disagreed with contemporary authors who argued that the direction of eye movement associated with the greatest periocular constriction to direct light in the eye affected with optic neuritis, a contribution that led to his receiving (undeserved) credit for the "Marcus Gunn pupil."

"Fortunately we can appeal, in such circumstances, to the character of the reaction of the pupil to light... The observation must be made with care; for it is only in very marked degree of amblyopia, from this cause that the pupil fails to act moderately well. But even in such slight cases, where the first contraction in the amblyopic eye seems perfect, there will be a difference in its failure to maintain the contraction under continued direct exposure to light." (12)

**SYMPTOMS AND SIGNS OF OPTIC NEURITIS**

**Pain**
The periorcular pain characteristic of optic neuritis has long been recognized. Netteship (2) and Swanzy (16) thought that more severe pain was associated with a worse visual prognosis. Hock postulated that the pain was the result of inflammation of the optic nerve sheath (17). The prevalence of pain in the large reported series of optic neuritis is summarized in Table 1. Perkin and Rose (3) reported that periorcular pain persisted longer than four weeks in 25% of patients.

**Vision loss**
Most authors have found central scotomas to be the most common pattern of field loss, followed by peripheral field constriction (2,3,11,12). Adie (18) and Traquair (19) argued that involvement of the central field was a prerequisite for diagnosis. Most series have emphasized central visual loss, with a small percentage of patients having altitudinal or hemianoptic vision loss (3,20). In a 1953 analysis of 100 consecutive optic neuritis cases, Chamlin (21) found that 25% of patients had non-central nerve fiber bundle defects. Positive visual phenomena were first reported by Gunn (12) and Traquair (19). Momentary sparks—spontaneous or evoked by sound or eye movement—were not described until the late twentieth century (22,23). Uhthoff (10), and later Gunn (12,15), described transient blurring of vision during exercise. Subsequently, Uhthoff's symptom has been recognized to be evoked by increased body temperature, and has been described in other optic neuropathies. Later studies (24–26) reported that patients with Uhthoff's symptom have an increased likelihood of MRI abnormalities and risk of developing multiple sclerosis.

**TABLE 1. Reported prevalence of pain in patients with optic neuritis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Percentage of patients with pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netteship (1944) (2)</td>
<td>61</td>
</tr>
<tr>
<td>Gunn (1904) (15)</td>
<td>33</td>
</tr>
<tr>
<td>Benedict (1942) (65)</td>
<td>50</td>
</tr>
<tr>
<td>Kurtland (1966) (66)</td>
<td>36</td>
</tr>
<tr>
<td>Bradly and Witty (1967) (67)</td>
<td>68</td>
</tr>
<tr>
<td>Hutchinson (1976) (68)</td>
<td>77</td>
</tr>
<tr>
<td>Perkin and Rose (1979) (3)</td>
<td>85</td>
</tr>
<tr>
<td>ONTT (1991) (28)</td>
<td>92</td>
</tr>
</tbody>
</table>
Fundus appearance
From the earliest descriptions of optic neuritis, the high prevalence of normal-appearing optic nerves at symptom onset has been well recognized. This diagnostic feature led to ready distinction of optic neuritis from other diseases of the optic nerve and retina. Uhthoff described disc swelling in only 5% of his optic neuritis patients (27). (The prevalence of disc swelling in large series reports is summarized in Table 2.) The prevalence of optic disc hemorrhages has been low (28). Lillie (29) in 1934 and Berliner (30) in 1935 described patients with retinal hemorrhages only with marked disc swelling.

The most significant diagnostic dilemma in the era before neuroimaging was the clinical distinction of optic neuritis from vision loss secondary to compressive optic neuropathy and papilledema. In Jackson’s 1900 textbook (50), these entities are not clearly distinguished. Paton (31,32) emphasized that in some cases of optic neuritis, the disc swelling can be as severe as that of papilledema. In 1922, Dandy (33) wrote that “intracranial tumors have too infrequently been missed by the over zealous enthusiasts searching for optic neuritis.” Together with Traquair (19) and Lillie (29), Dandy emphasized that the rapidity of vision loss and the type of visual field loss are the most reliable signs to distinguish these disorders. In general, papilledema has been easily distinguished from optic neuritis based on the relative preservation of vision, the associated symptoms (nausea and seizures), and the degree and persistence of the disc swelling (2,12,15,27). However, Walsh and Ford (34,35) emphasized that central scotomas, relatively rapid onset of vision loss, and spontaneous improvement could occur with compressive optic neuropathy.

Cerebrospinal fluid analysis
The importance of CSF analysis in optic neuritis was not recognized until the past half century. In 1939, Watkins (36) reported CSF findings in 40 patients with optic neuritis but did not tie the findings to multiple sclerosis. In subsequent series of optic neuritis patients, elevated levels of gamma globulin in the CSF were found in about 10-24% of patients and increased cell counts were found in 50% of patients (37,38). One of the six patients in the series of Sandberg and Bynke (37) demonstrated oligoclonal banding. Perkin and Rose found abnormal cell counts in 15% of their patients and elevated protein in 12% (3). The Optic Neuritis Treatment Trial (ONTT) showed that CSF analysis is a much less robust predictor than MRI of the future development of multiple sclerosis (39).

ETIOLOGY OF AND DIFFERENTIAL DIAGNOSIS OF OPTIC NEURITIS

“In more than half of the 120 cases I was able to find the etiological cause; where I did succeed in finding one, I diagnosed syphilis 14 times, hereditary tendency 11 times, multiple sclerosis 6 times, anomalies of menstruation 5 times, pregnancy 6 times, decided effects of cold 5 times, acute loss of blood 3 times, periorbitis orbitae 3 times, trauma twice, influenza twice, typhoid once, malaria once, polyneuritis once”—Uhthoff, 1904

“Probably no branch of neuro-ophthalmology has to its discredit the abundance of erroneous diagnoses as has optic neuritis.”—Cogan, 1904

The term “optic or retroocular neuritis” has had many different meanings. In the 1946 (first) edition of Clinical Neuro-ophthalmology by Walsh (41), “optic neuritis” includes hereditary, toxic, cancer-associated, infectious and inflammatory etiologies. In the 1980 edition Neurology of the Visual System, Cogan (40) includes inflammatory and vascular etiologies under “optic neuritis.” In the post-ophthalmoscope era, optic neuritis has been attributed to infections, hereditary disorders, sinus disease, compression and toxins. Before that era, it was attributed to “colds”, gout, rheumatic disease and tobacco (2,11,16,19,27). Many authors mistook the high rate of spontaneous resolution to reflect “successful treatments” such as sinus surgery or the elimination of a toxin. Here are some of the more prevalent ideas:

Sinus and tooth disease
The proximity of the sinuses to the optic nerves naturally led to the positing of a causative relationship (42,43). In 1897 Gunn wrote,

“In its passage through the optic canal, about 1 cm. in length, the nerve is exposed not only to inflammation extending to it from the bony walls and the periosseum, but also from the sphenoid sinus, only separated from it here by thin lamina of bone, which may be imperfect. It is probable that a considerable number of the cases of retroocular neuritis traced to exposure to cold are examples of inflammation attacking the nerve in this part of its course.” (12)

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Mild disc swelling</th>
<th>Marked disc swelling or disc swelling with hemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uhthoff (1904) (27)</td>
<td>100</td>
<td>5%</td>
<td>Not distinguished</td>
</tr>
<tr>
<td>Benedict (1942) (65)</td>
<td>90</td>
<td>9%</td>
<td>Not distinguished</td>
</tr>
<tr>
<td>Adie (1932) (18)</td>
<td>70</td>
<td>30%</td>
<td>Not distinguished</td>
</tr>
<tr>
<td>Hutchinson (1936) (68)</td>
<td>175</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Bradley and Whitty (1967) (67)</td>
<td>78</td>
<td>24.4%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Nikoskelainen (1975) (69)</td>
<td>240</td>
<td>18%</td>
<td>25%</td>
</tr>
<tr>
<td>Perkin and Rose (1979) (3)</td>
<td>151</td>
<td>35.1%</td>
<td>22.5%</td>
</tr>
<tr>
<td>ONTT (1991) (28)</td>
<td>448</td>
<td>35.3%</td>
<td></td>
</tr>
</tbody>
</table>
This was further supported by operative and autopsy evidence of active sinusitis extending through bony perforations to reach the optic nerve and cause focal inflammatory lesions. In 1933, Benedict (44) found that only 1 of 233 cases of retrobulbar neuritis examined at the Mayo clinic was attributable to sinus disease. In the initial review of the Johns Hopkins experience in 1931, Woods and Roland (45) found that 8% of patients had optic neuropathies resulting from sinus disease. However, in a 1952 review from the same institution (133 new cases), Bagley (46) did not find a single case that was attributable to sinus disease. Others believed that optic neuritis resulted from infections of the teeth and tonsils (47). Yet Traquair was unable to find a single case that resulted from tooth abscess or to have a "rhinogenic" etiology (19). In Gifford's 1931 review of 203 reported cases (48), he found only three cases convincingly caused by sinus disease. Nettleship (2), Percival (49), Gunn (12), and Swanzy (16) believed that inflammatory compression of the optic nerve within the optic canal was the cause of optic neuritis. This theory led to widespread use of optic canal decompression as a method of treatment.

**Syphilis**

Many cases of optic neuritis in the past were undoubtedly the result of syphilis (2). Buzzard believed that syphilitic optic neuropathy differed from optic neuritis in having a rapid progression to complete blindness (11). In the series of optic neuropathy patients from Johns Hopkins reported in 1931, 23 were attributed to syphilis (45). Those attributed to syphilis were almost always bilateral and associated with disc swelling. Walsh (50) concluded in 1956 that inflammatory optic neuritis was rare in acute syphilis, and that optic nerve involvement was a more prominent feature of the latter stages of the disease associated with more generalized neurologic disturbance. Nearly every other known infectious agent (bacterial, fungal and parasitic) has been reported to cause optic neuritis. "Tobacco amblyopia" represented 6% of 506 cases of optic neuropathy from a Johns Hopkins series reported in 1952 (46).

**Ischemic optic neuropathy**

The early papers on optic neuritis include cases that would today be considered to represent non-arteritic anterior ischemic optic neuropathy (NAION):

> "Perhaps the most common of the causes of pseudo-optic neuritis is ischemic optic neuropathy. Mimicking optic neuritis in almost every detail, ischemic lesions may produce central scotomas and pain on movements of the eye. One or both eyes may be affected. A diagnosis of ischemic optic neuropathy is to be expected in all patients who have their first attack in the middle of their life or later. Actually the differentiation from true optic neuritis is not of great importance since treatment of either is simply palliative."—Cogan, 1980

Even with current sophisticated diagnostic testing, ischemic optic neuropathy and optic neuritis may be hard to distinguish (51). Most of the literature concerning NAION is written after 1970, indicating that it was either less common or less well recognized in earlier times. Given that many patients considered in past days to have had "optic neuritis" did not recover vision and displayed substantial disc swelling, it is likely that AION was mistakenly included in older series of "optic neuritis."

**Hereditary, toxic, and nutritional optic neuropathies**

With the exception of Leber's hereditary optic neuropathy (LHON), hereditary optic neuropathies were rarely confused with optic neuritis. However, patients with optic neuritis and LHON both commonly present with the sudden onset of vision loss and central scotoma. Considering that at least 50% of patients with LHON lack a family history of the disease, it seems likely that LHON was overlooked in earlier series of patients reported to have optic neuritis.

Toxic and inflammatory optic neuropathies were often confused in the past. Treating physicians withdrew the offending agent, patients improved, and cause and effect were presumed. Since Traquair's original report in 1930 (19), in which he identified 1088 of tobacco-ambylophia cases from the Royal Infirmary in Edinburgh, this entity has been confused with optic neuritis. "Tobacco ambylophia" represented 6% of 506 cases of optic neuropathy from a Johns Hopkins series reported in 1952 (46).

**RELATIONSHIP OF OPTIC NEURITIS TO MULTIPLE SCLEROSIS**

As long as optic neuritis has been recognized, its relationship to multiple sclerosis has been appreciated. In 1893, Buzzard reported five patients with a history of disseminated or multiple sclerosis that had episodes of visual failure with recovery consistent with optic neuritis (11). In the early portions of the twentieth century, there was controversy over the relationship of optic neuritis to multiple sclerosis. In 1930, Adie asserted that multiple sclerosis accounted for all cases of optic neuritis:

> "The main purpose of this communication is to keep alive the discussion that has been proceeding spasmodically for forty years or more on the relationship of acute retrobulbar neuritis in general to disseminated sclerosis"—Adie (18)

Adie pointed out that optic neuritis might "be the only manifestation in a lifetime of the activity of the agent causing multiple sclerosis." (52) Percival (49) never saw a single case in which optic neuritis progressed to multiple sclerosis. Yet in 1934, Lillie (29) found that 75 (15%) of 500 cases of multiple sclerosis had optic neuritis as their initial event and nearly 200 developed it later in the course of their illness.

Over the first 80 years of the twentieth century, 30 studies reported the rate of the development of multiple sclerosis after an episode of optic neuritis (3). Perkin and Rose (3) emphasized the difficulty in interpreting this literature because of the inexact inclusion criteria, questionable neurologic evaluations at presentation, variable length of follow up, and criteria used to establish a diagnosis of multiple sclerosis. The rate at which multiple sclerosis developed has varied between 12% and 83% in
these series. Inadequate diagnostic criteria and clinical information prohibit valid comparisons of most of these retrospective studies. Recent prospective studies have yielded more valid, but not necessarily less confusing, information (summarized in Table 3).

**TREATMENT OF OPTIC NEURITIS**

The history of the treatment of optic neuritis centers on the effort over the past 50 years to determine whether systemic corticosteroids are valuable. Until the latter part of the nineteenth century, however, treatment revolved around the placement of solutions in the eye ("collyria"). Various compounds, including spittle, were rubbed in the eye (53). In the ninth century, Is-Haq wrote, "rubbing the lower part of the globe with a small instrument frees up the nerves destined for the motion of the pupil." He also pricked the muscles of the eye with a blunt needle and bled patients through the jugular vein. Frick's textbook in 1823 (6) suggests the use of emetics, identifying toxic substances, sinus surgery, and optic canal decompression. In 1899, Fuchs (55) suggested that "the treatment of the disease is that of neuritis in general; in the acute stage energetic diaphoresis proves particularly efficient." In the early part of the twentieth century, many patients were treated with sinus surgery or optic canal decompression. Optic canal decompression was still suggested for the treatment of retrobulbar neuritis as recently as 1952 (56). In 1933, Benedict (44) recommended treatment with intravenous typhoid vaccine, postulating that this increases the vascularity of the tissues (the same mechanism proposed to explain the apparent benefit gained from operating on non infected sinuses). In 1941 Duke-Elder (57) directed treatment at the reduction of local edema and advocated the use of salicylates, sweats and open bowels. In 1941, Duggan (58) described, under the title of retrobulbar neuritis, what was probably ischemic optic neuropathy, and recommended intravenous injections of sodium nitrite, intramuscular acetylpipline, and inhalations of amyl nitrite.

**Corticosteroids**

By the 1930s, most experts had begun to shift their attention from intoxications and infections to primary inflammation of the optic nerve as the potential mechanism of disease. Soon after their introduction in the 1950s, corticosteroids were used to treat optic neuritis. Adrenocorticotropic hormone (ACTH) became a popular treatment primarily based on the work of Rawson (59). Benefit of ACTH was determined based on near acuity measurements at one month after onset of optic neuritis. However, Giles (60) and Bowden et al. (61) found no significant benefit two years after steroid treatment, but did show that it significantly hastened visual recovery in the first two to three weeks. Bird et al. (62) found that retrobulbar injections of triamcinolone produced faster recovery but no long term differences between treated and untreated patients. In the 1969 edition of their book, Walsh and Hoyt concluded that ACTH was not beneficial (63).

It was not until the last 15 years that the ONTT (64) showed, through a large randomized trial, that oral prednisone treatment, in milligram per kilogram body weight doses, was ineffective and promoted recurrences of the

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**TABLE 3. Summary of prospective studies reporting the proportion of optic neuritis patients developing multiple sclerosis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Follow-up (yrs)</th>
<th>Proportion developing MS, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landy (1983) (71)</td>
<td>Australia</td>
<td>range 1-29</td>
<td>71%</td>
<td>By life-table analysis, probability of MS by 15 years was 75%</td>
</tr>
<tr>
<td>Francis et al. (1987) (72)</td>
<td>U.K.</td>
<td>mean 11.6</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Rizzo and Lessell (1988) (73)</td>
<td>New England</td>
<td>mean 14.9</td>
<td>58</td>
<td>By life-table analysis, probability of MS by 15 years was 74% for women and 34% for men</td>
</tr>
<tr>
<td>Sandberg-Wollheim et al. (1990) (74)</td>
<td>Sweden</td>
<td>mean 12.9</td>
<td>38</td>
<td>By life-table analysis, probability of MS by 15 years was 45%</td>
</tr>
<tr>
<td>Morrissey et al. (1993) (75)</td>
<td>U.K.</td>
<td>mean 5.3</td>
<td>normal MRI: 6</td>
<td>MRI white matter lesions were associated with development of MS</td>
</tr>
<tr>
<td>Jacobs et al. (1997) (76)</td>
<td>New York</td>
<td>range 4 mo. to 19 years</td>
<td>abnormal MRI: 82 normal MRI: 16</td>
<td>MRI white matter lesions were associated with development of MS</td>
</tr>
<tr>
<td>Optic Neuritis Study Group (O.N.T.T.) (1997) (77)</td>
<td>U.S.A. and Canada</td>
<td>5</td>
<td>abnormal MRI: 38 normal MRI: 16</td>
<td>MRI white matter lesions were associated with development of MS</td>
</tr>
</tbody>
</table>
optic neuritis. That trial confirmed that intravenous corticosteroids (methylprednisolone 1 gm/day) for three days, followed by prednisone (mg/kg body weight/day) for eleven days, accelerates visual recovery but does not improve final visual outcome.

Acknowledgment: I am grateful for the helpful suggestions of Dr. Jeffrey Odell.

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Letter to the Editor

Comparison of the ONTT Intravenous Group and the CHAMPS Placebo Group

To the Editor:

I have been asked on numerous occasions how the outcome data regarding development of multiple sclerosis (MS) from the Optic Neuritis Treatment Trial (ONTT) \(^{(1)}\) compare with the outcome data from the CHAMPS trial \(^{(2)}\). In particular, how does the risk of development of clinical definite MS (CDMS) in the ONTT intravenous group patients with two or more brain magnetic resonance imaging (MRI) lesions compare with the risk of CDMS in the CHAMPS placebo group patients who presented with optic neuritis (and according to entry criteria had two or more brain MRI lesions)?

In both trials, the aforementioned groups received a course of intravenous methylprednisolone (IVMP) 1000 mg/d for 3 days followed by oral prednisone 1 mg/kg/d for 11 days, followed by a short taper. In the ONTT, the intravenous therapy was administered in four doses of 250 mg/d, whereas in CHAMPS 1000 mg was administered in a single daily dose. Treatment was initiated in the ONTT after an average of 4 days (maximum 8 days) of symptoms, compared with 9 days (maximum 14 days) in CHAMPS.

In order to compare the CDMS rates between the two trials, several differences in the study design and analytic approach must be accounted for. First, the definition of CDMS in the ONTT did not include fellow eye optic neuritis, whereas in CHAMPS the occurrence of optic neuritis in the fellow eye was considered sufficient for a diagnosis of CDMS. Second, ONTT patients had formal protocol-specified neurologic exams only at baseline, and 6, 12, and 24 months, whereas in CHAMPS protocol-specified exams were performed at 6-month intervals plus at times of new onset of symptoms. Thus, some patients in the ONTT who were classified as probable MS (meaning that symptoms consistent with a demyelinating event lasting more than 24 hours occurred but abnormality was not documented on a subsequent exam) likely would have been classified as CDMS if a protocol examination had been performed at the time of symptoms. Third, the life-table estimates in CHAMPS and the ONTT were computed differently; in CHAMPS, the life-table analysis of time to CDMS began 30 days after the onset of study drug (Avonex [Biogen; Cambridge, MA] or placebo) because by the protocol CDMS could not occur before this time point (which on average was 49 days from the start of symptoms), whereas the ONTT analysis used the randomization date as the starting point (which on average was 4 days from the start of symptoms).

The 2-year cumulative probability of CDMS was 37% in the 97 CHAMPS placebo group patients presenting with optic neuritis. In the ONTT, after adjusting the life-table estimate for the 37 MRI-positive intravenous group patients so as to be more consistent with the CHAMPS CDMS diagnostic criteria and the life-table analytic method, the 2-year estimate of CDMS is 28%. The 95% confidence interval for this estimate is 14 to 44%, which includes the CHAMPS estimate of 37% \((P = 0.31)\). Thus, much of the difference in the 2-year rates of CDMS in the ONTT and CHAMPS is accounted for by differences in study design. The remaining difference is consistent with chance, which is not surprising considering the relatively small number of ONTT patients suitable for a comparison with the CHAMPS cohort. Whether there could be any difference related to the earlier onset of treatment in the ONTT or the dosage schedule cannot be determined. Finally, although I conclude that there is unlikely to be a true difference in the rates of CDMS comparing the ONTT and CHAMPS, one must always be cautious in comparing results from treatment groups in nonconcurrent studies because this can lead to erroneous conclusions \((3,4)\).

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Jaeb Center for Health Research
Tampa, Florida

REFERENCES

The Fifth European Neuro-Ophthalmological Society (EUNOS) Meeting, Tübingen, Germany, July 22–26, 2001

Jonathan D. Trobe, MD

The Fifth European Neuro-Ophthalmological Society (EUNOS) Meeting drew more than 200 attendees from 33 countries to Tübingen, Germany, July 22 through 26, 2001. The meeting was held at the University of Tübingen, which was founded in the 14th century and is the second oldest university in Germany (after Heidelberg).

The meeting’s organizers, Susanne Trauzettel-Klosinski, Helmut Wilhelm, Barbara Wilhelm, and Eberhart Zrenner of the University’s Department of Pathophysiology of Vision and Neuro-ophthalmology, put together an impressive program that included 46 papers, 50 posters, and 25 invited lectures. (Abstracts are published in the *Journal of Neuro-ophthalmology* 2001, 24:1–102).

A preliminary half-day session was a refresher course on the pupil, neuroradiology, oculomotor disorders, and the electroretinogram (ganfeld and multifocal). The first day concluded with a festschrift in honor of Bill Hoyt’s 75th birthday, given by his former fellows. More than 25 former fellows participated, 11 of whom delivered short papers (Mike Sanders, Anja Palmowski, Bernd Schlicke, Klara Landau, Ivor Levy, Chris Kennard, Gordon Plant, Patricia Logan, Kay-Uwe Hamann, Paul Riordan-Eva, and Guntram Kommerell). Recalling his triumphs and humiliations as one of Bill’s earliest fellows, Kommerell called Hoyt the “semital figure for neuro-ophthalmology in Europe.”

Thereafter, the meeting was divided into five topic sessions centered around invited lectures designed to update the audience on critical issues.

**PERCEPTUAL DISORDERS OF VISION**

In a session devoted to perceptual aspects of vision, Hanspeter Mallot (Tübingen) and Guy Orban (Louvain) introduced recent experimental work on object and motion processing. Hans Otto Karnath (Tübingen) argued that human lesion studies of unilateral neglect suggest that spatial awareness in humans is processed in the right superior temporal cortex rather than in the posterior parietal cortex, as has been assumed from monkey studies. He reasoned that the emergence of language in the left temporal cortex of humans is associated with a shift of spatial awareness from right parietal to right superior temporal cortex. Dominic Mort (London) reported on scanpath strategies; Avinoam Safran (Geneva) reported on plasticity in the visual cortex; Susanne Trauzettel-Klosinski (Tübingen) reported on reading strategies, as observed with scanning laser ophthalmoscopy, in patients with various visual impairments; François...
Vital-Durand (Lyon) updated the audience on visual development in infants; and Lea Hyvarinen (Helsinki) reported that sessions of flicker stimulation of the blind hemifield in one patient eventually resulted in improvement in vision in that field, an argument that left several listeners unconvinced.

PERIMETRY

In a session dedicated to perimetry, Lars Frisén (Göteborg) posited that the newest technological developments in stimulus presentation are further exposing the subjective—and therefore unreliable—nature of this test. Given the sophisticated imaging tools we now have for locating structural and even functional brain impairments, he also suggested that future perimetric devices may find their greatest utility in providing a quick overall index of function rather than spatial detail. Robert McFadzean (Glasgow) recapitulated the current views on the topographic organization of visual cortex, based on lesional studies in primates and humans, and on functional magnetic resonance imaging (MRI). Ulrich Schiefer (Tübingen) delivered an eloquent paean to Elfriede Aulhorn, the former Tübingen professor who died prematurely in 1991. She largely developed the famed Tübingen Manual Perimeter and left a rich legacy of visual field data. Pinar Aydin (Ankara) reported that high-pass perimetry provides valuable information in patients with dysthyroid optic neuropathy. Freddie Huber (Zurich) presented a report of a patient with an episode of full-field dyschromatopsia (“everyone appeared brownish-yellow”) signaling the presence of a right parieto-occipital glioblastoma. Surprisingly, formal visual fields were normal. Shlomo Dotan (Jerusalem) described cases of tamoxifen-, vigabatrin-, and sildenafil-induced visual disturbances. Eedy Mezer (Toronto) used a sweep visual evoked potential (VEP) test to measure contrast sensitivity objectively in children with papilledema and found that peak contrast sensitivity was slightly, but not significantly, lower in subjects in the papilledema group than in control subjects, perhaps owing to small sample size.

ASSESSMENT OF VISUAL FUNCTION

In a session dedicated to advances in methods of assessing visual function, Michael Bach (Freiburg) proposed that newer computerized methods of measuring visual acuity, contrast sensitivity, and stereoacuity provide more accurate information. Candice Chen, a medical student at Columbia University (New York),
representing the efforts of the psychophysics/electrophysiology group there to improve the reliability of the multifocal VEP, showed that adding recording electrodes and channels increases the ability of this method to detect optic nerve disorders. Noting that patients with impaired pursuit eye movements often complain of reduced vision, Thomas Harmeier (Tübingen) measured dynamic visual acuity with horizontally moving Landolt C's and found a marked deficit in patients with impaired pursuit as compared with control subjects. Josephine Shallo-Hoffmann (Fort Lauderdale) found that, in screening 102 preschool children, more could complete the Lea Symbol Visual Acuity and Lang Stereoaucuity Tests than the standard Tumbling E and Randot E Tests.

**BRAIN IMAGING**

In a minisymposium on brain imaging, Rainer Goebel (Maastricht) provided evidence that magnetoencephalography (MEG) improves the temporal resolution of functional MRI in vision-related event mapping. Simo Vanni (Toulouse) also showed that MEG is a useful tool in localizing cortical regions responsible for visual processing. Philippe Demaerel (Louvain) presented MRI follow-up of 19 children with anterior visual pathway glioma and showed that in seven of eight patients who were untreated, tumor size did not increase; in 10 patients treated with vincristine and carboplatin, the tumor shrunk in six and remained unchanged in one. In essence, the prognosis was excellent. Mark Kupersmith (New York) found MRI enhancement of the affected optic nerve in 101 of 107 patients (95%) with optic neuritis; a number that appeared astounding high to others with similarly heavy caseloads. There was no correlation between the location of the enhancement (orbit, canal, or intracranial segments) and the severity of visual loss or its outcome. Dieter Schmidt (Freiburg) presented evidence that a dark halo around the lumen and luminal thickening on color-coded Duplex sonography are the most specific sonographic signs of temporal arteritis. Jette Frederiksen (Glostrup, Denmark) found reduced activation of visual cortex on functional MRI scans in patients with optic neuritis as compared with control subjects.

**THERAPEUTICS**

In a session on therapeutics, Helmut Wilhelm and Gerd Becker (Tübingen) reviewed the visual outcomes of 49 patients with optic nerve sheath meningiomas managed at the University of Tübingen from 1994 to 2000 with a mean follow-up period of 52 months. Of 39 patients treated with stereotactic fractionated radiation therapy, none showed visual deterioration and 14 (36%) showed some visual improvement. There were no complications. Of 10 patients observed without treatment, 7 (70%) showed visual deterioration, 2 (20%) remained stable, and 1 (10%) improved. The conclusion is obvious: this treatment works and it is not dangerous. Bernhard Schuknecht (Zurich), a neuroradiologist, presented the results of intra-arterial injection of urokinase in 19 consecutive patients with acute central retinal artery occlusion within 12 hours of event onset. Complete visual recovery occurred in 26.3% of patients. The authors noted that this outcome is better than that of two previously reported large series (12.9% and 17.6%) and of a meta-analysis of all prior reports (14%). A large prospective trial is underway in Europe in which patients will be randomized to endovascular thrombolysis, systemic thrombolysis, or no therapy. Mark Kupersmith (New York) reviewed the records of 94 patients with "ocular myasthenia gravis" and found that only 4 of 58 patients
(7%) treated with prednisone went on to develop "generalized myasthenia gravis" as compared with 13 of 36 untreated patients (36%). This is provocative information and may warrant a prospective trial.

OPTIC NEUROPATHIES

In a session devoted to optic nerve disorders, Christiane Alexander (London) proposed that mutations in the OPA1 gene are responsible for dominant optic atrophy. In his interpretation of the multicenter trials of "disease-modifying therapy" in multiple sclerosis, Jonathan Trobe (Ann Arbor) acknowledged that the interferons and glatiramer have reduced relapse rates and the accumulation of MRI signal abnormalities, but reminded the audience that no drug in any trial has yet shown an impact on neurologic disability. Jost Jonas (Erlangen) proposed that the disc excavation of glaucoma differs from that following arteritic ischemic optic neuropathy in producing parapapillary retinal pigment epithelium (RPE) atrophy.

NEURAL REGENERATION

In a session on neural regeneration, Christian Vorwerk (Leipzig), Solon Thanos (Münster), and Emiko Adachi-Usami (Chibar, Japan) presented laboratory studies that show promise in overcoming the central nervous system inhibitors of regeneration, but it was apparent that clinical applications are a long way off.

RETINA

In a session devoted to the retina, Eberhart Zrenner (Tübingen) pointed out that the RPE has four functions: 1) phagocytosis, 2) retinol transport and storage, 3) ionic homeostasis, and 4) protection from light damage. The key to treating most RPE disorders is finding, cloning, and discovering the function of the aberrant genes. Papers by Hendrik Scholl (Tübingen), Herbert Jaegle (Tübingen), and Anja Palmowski (Hamburg) pointed out how refinements in the ERG, including the multifocal version, have improved diagnostic sensitivity. Florian Gekeler (Tübingen) convinced the audience that the Tübingen subretinal prosthesis is feasible but still not able to produce adequate cortical responses.

PUPIL

The pupil got its own minisymposium, introduced by an elegant summary of its quirks by Stephen Smith (London), and followed by a review by Barbara Wilhelm (Tübingen) of the utility of pupillography in refined diagnosis of Adie's and Horner's syndromes, objective perimetry, and in measuring sleepiness. Fion Bremner (London) compared threshold and pupil perimetry in eight patients with optic neuritis and found much better recovery of visual thresholds than pupillary constriction in the same stimulus positions. He postulated that remyelination was better in the larger retinogeniculate (vision) than in the smaller retinotectal (pupillary) axons. By testing a patient with a dorsal midbrain syndrome with various pupillographic stimuli, John Barbur (London) suggested that the central sympathetic inhibition of the pupillary response is mediated directly via the Edinger-Westphal nuclei and does not require the pretectal pathways. In a patient with botulism, Helmut Wilhelm (Tübingen) found, with pupillography, that the pupils constricted well to direct light but not to a near target ("inverse light: near dissociation") and that accommodation was lost. His explanation: the toxic has higher affinity for the ciliary ganglion neurons subserving accommodation and the near response than the light response. Do we really understand these pathways?

EYE MOVEMENTS

The session on eye movement disorders brought in Charles Pierrot-Deseilligny (Paris) for a relatively elementary overview of nuclear and supranuclear disorders, followed by an update from Detlef Kompf (Lübeck) on the role of the human frontal eye fields. According to the latest work, they are involved not only in all types of voluntary saccades and saccadic pursuit, but also in visuospatial function (ordinarily assigned to parietal lobe) and short-term memory (ordinarily assigned to limbic pathways). Hans-Peter Thier (Tübingen) described how his single-unit recordings of monkey cerebellum suggest how populations of Purkinje cells con-
Closing banquet in the Cloister of Bebenhausen, built in 1183 for the order of Zisterzienser and transformed in 1802 into a hunting castle for the Wuerttenberg kings.

tribute to saccadic adaptation. Using tracers injected into extracocular muscles, Jean Büttner-Ennever (Munich) found that large motoneurons located within motor nuclei innervate twitch fibers, whereas smaller motoneurons located around the edge of the nuclei innervate non-twitch fibers. Irene Gottlob (Leicester) surveyed the families of patients with spasmus nutans and infantile nystagmus in Philadelphia and found that the patients with spasmus nutans were significantly more often Hispanic or African-American, exposed to lower home luminance, and from poorer families with higher prevalence of psychiatric and social disorders (alcoholism, drug abuse).

One evening was devoted to viewing the 50 posters. With Rhine wine glasses in hand, attendees moved through the exhibit guided by tour leaders, who helped to focus the 5-minute explanations of each poster presenter.

There was a bus trip to a Hohenzollern castle on the top of a mountain, and a festive dinner in a 12th century cloister. The organizers secured a grant from the German government to underwrite the expenses of 10 neuroophthalmologists making their first trips abroad from Russia and other Eastern European countries. They discovered a gracious medieval setting, a high level of scientific discussion, state-of-the-art audiovisual facilities, a superbly organized meeting, and balmy weather—an unexpected feature to top off an impressive effort by the Tubingen group.

Acknowledgment: The author gratefully acknowledges Shilomo Dotan, MD, and Jens Reinhardt for photographs.
**Book Reviews**

Section Editor: Barrett Katz, MD, MBA

**Neuro-Ophthalmology: Diagnosis and Management**

**Scope:** This basic text presents a thorough and clinically useful overview of neuro-ophthalmologic diseases. Included are helpful reviews of neuroanatomy, visual fields, ancillary tests, and electrophysiology. As a volume of more than 700 pages, this book is more extensive than an introduction but less extensive than a definitive reference. The major focus is on clinical differential diagnostic and management, with supplementary discussions of neuroanatomy, physiology, and ancillary studies used in neuro-ophthalmology.

**Contents:** The book is divided into four main sections: history and examination, afferent disorders, efferent disorders, and headache. The afferent and efferent sections are subdivided neuroanatomically, and lead the reader from anterior visual pathways to higher cortical dysfunction. Each subsequent chapter provides an organized and thoughtful presentation of a topical disorder by covering pertinent review of the anatomy, then pathophysiology, clinical presentations, differential diagnosis, relevant diagnostic-imaging studies, discussion of specific disease entities, and management. There are also symptom-based discussions that emanate from the patient report precipitating the physician visit.

Each subsection succinctly discusses the disease process and, where appropriate, includes fundus photos, neuroradiologic illustrations, and tables of distinguishing features. Important differential characteristics are emphasized, which clarify information for the reader. In addition, each subsection is followed by an up-to-date bibliography.

The initial section of two chapters teaches the history and examination. The subsequent section deals with visual loss and dysfunction. Chapter 3 encompasses a topical overview of afferent disorders, visual pathways, visual field, and electrophysiologic diagnostic testing. Chapter 4 presents a useful discussion of retinal disorders that mimic optic neuropathies. Chapters 5 through 8 focus on topographic neuro-ophthalmology from nerve to cortex, and in particular update the prognosis and management of optic neuritis. The last four chapters elaborate on diseases of higher cortical function and the entities of transient visual loss, functional visual loss, and visual hallucinations and illusions.

The third major section discusses efferent disorders including ocular motility-related cranial neuropathies and papillary, eyelid and facial nerve, and movement abnormalities. The last chapter of this section is devoted to orbital disease. The final section focuses on headache, facial pain and disorders of facial sensation.

**Strengths:** The text is particularly useful for the all-in-one systematic overview of the clinical field, from anatomy to management. The thoroughness of disease discussion (by the use of key charts, tables, outlines, and clinically significant photos and neuroimaging scans) is commendable. The brief yet pertinent references direct readers to more detailed investigations and primary sources. The publisher’s use of chapter numbers on each page allows one to efficiently scan for information.

**Deficiencies:** The length of the book may overwhelm residents looking for one resource for their 3-month rotation. Although the book focuses on diagnosis and management, it may do so at the expense of neuroanatomy, visual field testing, neuroimaging, and electrophysiology.

**Recommended audience:** Residents in ophthalmology and neurology and fellows in neuro-ophthalmology would benefit from this text.

**Ralph A. Sawyer, MD**
Washington, DC

**Atlas of Eyelid and Conjunctival Tumors**

**Scope:** This authoritative atlas presents histopathologic groups of tumors of the eyelid, conjunctiva, and caruncle. It is one of three volumes of an atlas of ocular tumors by a world-renowned husband and wife team with 25 years of experience in ophthalmic oncology at the Wills Eye Hospital. They have published their experience with common and rare lesions in a pictorial reference that provides a broad overview of neoplasia in the eyelid and conjunctiva, with special emphasis on the malignant tumors and their surgical management. Many of these lesions are common and benign, but others are malignant and locally invasive or metastatic and necessitate a thoughtful and rational management approach. The book is intended to aid the ophthalmologist or dermatologist in the diagnosis of these lesions so that appropriate therapy can be instituted.

**Contents:** The book is divided into two parts: lesions of the eyelids and those of the conjunctiva. The atlas...
chapters are divided into histopathologic types including nonmalignant and malignant epidermal lesions, sebaceous gland tumors, sweat gland tumors, hair follicle tumors, melanocytic tumors, neural tumors, vascular tumors, lymphoid tumors, cystic lesions, and inflammatory lesions of the eyelids. Fifteen of the twenty-five chapters in this text deal with lesions of the eyelids. The last ten chapters cover benign and malignant tumors of the conjunctival epithelium, melanocytic tumors, vascular, fibrous, neural, lymphoid, and leukemic tumors, and tumors of the cataract. Each lesion type is described in a concise manner with respect to origin, clinical and histologic appearance, differential diagnosis, treatment, and prognosis, and is followed by clinical, histopathological, and surgical photographs.

Strengths: A total of 1,056 clinical and histopathological color photographs clearly convey the characteristics of these lesions. The large number of images is necessary for identifying tumors of the ocular adnexa, where pattern recognition is an important diagnostic tool. Surgical perioperative photographs showing treatment techniques are adequately presented, and follow-up procedures in the management of recurrence are discussed. This is an informative atlas that presents both common and rare tumors.

Deficiencies: The discussion of several less important lesions is thin.

Recommended audience: General ophthalmologists, oculoplastic surgeons, and dermatologists will benefit from this text.

Critical appraisal: This resource is a well-illustrated and portable atlas that is authoritative in its presentation. Although wide in its scope, the text is a pleasure to read and even flip through. It is a shame that a pocket edition is not available for all of our residents.

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George Washington University
Washington, DC

Atlas of Intraocular Tumors,

Scope: This is a comprehensive picture atlas, part of a three-part series on ocular tumors by the authors. They are recognized as ultimate authorities on the subject of ocular tumors and this work is a collective presentation of their 25 years of experience in this field. The focus of the book is to be a ready reference for recognition of various intraocular tumors and related conditions. A slide collection of cases is used to achieve this goal. A concise description of both the rare and the common tumors with clinical presentation, clinical examination, histopathology, and references is given. The predominant emphasis is on the clinical presentation and pathology of pigmented tumors, which reflects the authors’ deep interest in the subject. The design of the book allows the ophthalmologist to correctly diagnose the lesions so that appropriate therapy and management are instituted in a timely way.

Contents: The book is organized into three parts. The first part covers tumors of the uveal tract; the second deals with tumors of the retina and optic disc; and the last part encompasses miscellaneous intraocular tumors. The first section is the largest part and contains 14 chapters describing congenital uveal lesions, iris nevi, iris cysts, and iris melanomas. Five chapters are devoted solely to posterior uveal melanomas and their clinical features, pathology, diagnosis, management, and those tumors simulating posterior uveal melanomas. In the second part, two chapters deal with retinoblastoma and simulating lesions. The other two chapters cover vascular lesions and glial tumors of the retina and optic disc. Finally, the last and shortest section of the atlas contains four chapters that describe congenital retinal pigment epithelium (RPE) hypertrophy and hyperplasia, combined hamartomas of the retina and RPE, and adenoma and adenocarcinoma of the retina and RPE. Other chapters detail tumors of the nonpigmented ciliary epithelium, intraocular lymphoid tumors, and leukemia. Finally, a rather short chapter covers the surgical approaches to intraocular cases.

Strengths: The atlas displays more than 1482 illustrations and photographs culled from the authors’ experience in handling cases of neoplasms from around the globe. These clinical and histopathologic photographs are, with few exceptions, of excellent quality and leave the reader feeling comfortable with the characteristic appearance and presentation of these entities. Moreover, some lesions are supplemented with detailed pictures of the fundus, anterior segment, radiographic images, fundus illustrations, fluorescein angiograms, and external photographs.

Deficiencies: The last chapter (22), describing the various surgical techniques used in the management of intraocular tumors, deals with the topic in a rather cursory manner. Some of the illustrated surgical approaches are deficient in scope. A broader review of surgical techniques and their references is recommended for the reader.

Recommended audience: Ophthalmology residents, practicing ophthalmologists, and ocular oncologists. I have found it helpful in several difficult cases I recently managed.

Critical appraisal: At your fingertips is a detailed compendium of the presenting features and appearance of intraocular tumors composed by authoritative sources. This belongs in the library of every ophthalmology training program.

Craig E. Geist, MD, MS, FACS
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Scope: This is a comprehensive picture atlas, part of a three-part series on ocular tumors by the authors. They are recognized as ultimate authorities on the subject of ocular tumors and this work is a collective presentation of their 25 years of experience in this field. The focus of the book is to be a ready reference for recognition of various intraocular tumors and related conditions. A slide collection of cases is used to achieve this goal. A concise description of both the rare and the common tumors with clinical presentation, clinical examination, histopathology, and references is given. The predominant emphasis is on the clinical presentation and pathology of pigmented tumors, which reflects the authors’ deep interest in the subject. The design of the book allows the ophthalmologist to correctly diagnose the lesions so that appropriate therapy and management are instituted in a timely way.

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Scope: This is the third of three volumes of a work entitled Atlas of Eyelid and Conjunctival Tumors, Atlas of Intraocular Tumors, and Atlas of Orbital Tumors. It is designed to aid the ophthalmologist and general physician with the recognition of orbital inflammatory and neoplastic conditions. It is a short but rather detailed picture atlas of both common and rare orbital lesions.

Contents: This atlas is divided into types of orbital lesions based on their histopathology and anatomic location within the orbit. The book is made up of 16 chapters, of which cystic and vascular lesions constitute a large portion of the contents. A concise description of the clinical entities is given and clinical cases are presented with external photographs, orbital/cranial radiographs, fundus photographs, and histopathology to illustrate the cases.

Strengths: The atlas contains an excellent mix of clinical, radiographic, and histopathologic photographs. Rare and common tumors alike are presented with a broad overview. This work is designed to be a user friendly and readily accessible text that will make the ophthalmologist’s job a little easier. References are readily provided for more detailed reading, but the most important information is within the atlas.

Deficiencies: Intraoperative photographs and descriptions of surgical approaches are deficient. Illustrations of surgical approaches are treated in a cursory manner at the end of the book and would be better handled with clinical photographs of actual cases and a reference to an orbital surgical text.

Recommended audience: Ophthalmologists and other physicians who deal with orbital diseases. Residents in training will find it invaluable for study and for use in the clinics.
Critical appraisal: This book will be especially welcome in handling those difficult cases with multiple symptoms, numerous orbital radiographs, and surgery or medical management. This atlas provides the clinical correlation and treatment pearls that are often lacking in an exhaustive text.

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Scope: This is an introductory book designed to be a comprehensive atlas of strabismus and pediatric ophthalmology surgery. The text discusses surgical and ocular anatomy, preoperative planning, and surgical techniques. It adequately covers nearly all clinical situations encountered in a pediatric ophthalmology practice and offers thoughtful discussion of appropriate preoperative preparation and surgical management.

Contents: The book consists of 16 chapters. The early chapters describe surgical planning, surgical considerations, surgical anatomy, and conjunctival incisions in a generic fashion applicable to all types of strabismus procedures. Two chapters are devoted to retractor muscle weakening and strengthening procedures. Specific chapters on inferior oblique and superior oblique surgery follow, with ensuing titles that include adjustable suture techniques, transposition, and applications of Botox injection. Specific attention is directed to complications of strabismus surgery and help with difficult but common problems. Additional chapters discuss childhood strabismus surgery, pediatric glaucoma, and lacrimal procedures, although these are not particularly comprehensive.

Strengths: This overview is a superb text for the beginning ophthalmology resident, the pediatric ophthalmology fellow, and the comprehensive ophthalmologist who wishes to learn strabismus surgery. It is helpful for the subspecialty pediatric ophthalmologist who wants to review less common strabismus surgeries. Discussions of indications for surgery and preoperative planning are extremely appropriate and will assist all surgeons.

Deficiencies: The book is several years old (and out of print). As a result, some newer procedures are not adequately described. For example, prism adaptation is not discussed in the management of partially accommodative esotropia or esotropia with high AC/A ratio. In addition, the Foster modification of the Jensen procedure is not mentioned. Finally, the section on pediatric cataract surgery is outdated. Although the section on strabismus surgery planning is superb, the author tends to be dogmatic in areas that are controversial. For example, the author states that "patients with esotropia at near of up to 15 prism diopters more than at distance can have bilateral medial rectus resections for the near deviation without running undue risk of overcorrection at distance." Many would disagree with this statement, believing that prism adaptation for the near deviation is a more accurate method of correction. Similarly, there is no consensus that bilateral medial rectus muscle recessions are advisable for all patients with divergence excess exotropia, without respect to whether they have the pseudodivergence type, the true divergence excess type, or a high AC/A. The common but older adjustable suture technique using a noose is described, but the simpler, more standard, widely accepted, bow-tie knot is not discussed. Finally, the author does not acknowledge the controversy over whether dissociated vertical deviation should be treated with bilateral hang-back superior rectus recession or unilateral hang-back recession in the preferred eye.

Recommended audience: Comprehensive ophthalmologists and pediatric ophthalmology fellows. It should be a part of every ophthalmology training program's library.

Critical appraisal: This work can be a stand-alone atlas for pediatric strabismus surgery. Chapters on pediatric cataract surgery and pediatric glaucoma surgery should be significantly expanded.

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Nashville, Tennessee


Scope: This is a multiauthored, hardcover, 244-page text that is part of a series entitled Developments in Ophthalmology. It is designed to provide the reader with an understanding of the pathophysiology of common immune-mediated disorders of the eye.

Contents: The text is divided into 15 chapters. The first chapter introduces general principles of immunoophthalmology. The following chapters cover the immunology of Graves' ophthalmopathy, the lacrimal gland and tear film, allergic conjunctivitis, ocular uveitis, and immune-mediated disorders of the eye. Finally, the section on pediatric cataract surgery is outdated. Although the section on strabismus surgery planning is superb, the author tends to be dogmatic in areas that are controversial. For example, the author states that "patients with esotropia at near of up to 15 prism diopters more than at distance can have bilateral medial rectus resections for the near deviation without running undue risk of overcorrection at distance." Many would disagree with this statement, believing that prism adaptation for the near deviation is a more accurate method of correction. Similarly, there is no consensus that bilateral medial rectus muscle recessions are advisable for all patients with divergence excess exotropia, without respect to whether they have the pseudodivergence type, the true divergence excess type, or a high AC/A. The common but older adjustable suture technique using a noose is described, but the simpler, more standard, widely accepted, bow-tie knot is not discussed. Finally, the author does not acknowledge the controversy over whether dissociated vertical deviation should be treated with bilateral hang-back superior rectus recession or unilateral hang-back recession in the preferred eye.

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BOOK REVIEWS


Scope: This multi-authored book covers the basic science and clinical applications of mucosal immunology, with several chapters specifically dealing with ocular immunology. Because it is a comprehensive overview of mucosal immunology, much of the book does not deal with ocular immunology specifically; therefore, the text will more likely appeal to the immunologist and basic scientist rather than to residents or clinicians. Furthermore, few practical clinical applications or methods of treating immunologic disease of the ocular surface are included.

Contents: The text is divided into 18 chapters. The first three chapters deal with basic immunology of mucosal tissue in general, and are cogent reviews of the current state of knowledge of the mucosal and secretory immune system. Six chapters deal specifically with ocular immunity and review knowledge in this area comprehensively. It becomes apparent that much more is known about gastrointestinal immunity than about ocular immunity; hence, the authors include chapters on celiac disease, arthritis, and T-cell differentiation in the gastrointestinal tract. The number of references within each chapter is overwhelming, as evidenced by 395 references included in a 17-page chapter about the ocular secretory immune system.

Strengths: This book provides outstanding compilations of the current state of the art of the mucosal immune system, with some focus on the ocular aspects of this system. Information concerning the induction of oral tolerance for the treatment of uveitis is up to date. Much of the information in the book is based on experimental animal data, especially the chapters regarding ocular immunology. This book is an excellent reference for anyone interested in developing clinical research protocols based on available experimental data.

Weaknesses: The text is too technical and experimentally oriented to provide the clinician with information that will change the current treatment of patients. For example, the chapter about the effect of oral tolerance on corneal allograft survival focuses exclusively on murine corneal transplantation, with the last few paragraphs hinting toward potential clinical use. The reader is left with the impression that there is little known about the mucosal ocular immune system that can be applied clinically. Most chapters deal with nonocular information, and there is little attempt to make these chapters relevant to the ophthalmologist. No clinical chapter covers the current state of knowledge concerning allergic conjunctivitis, trachoma, viral conjunctivitis, or herpes simplex. Inclusion of information regarding these diseases, in which the mucosal immune system may play a strong role, would have made this book more useful for ophthalmologists and might have integrated the basic science chapters with relevant clinical issues.

Recommended audience: Ophthalmologists interested in ocular surface disease, those interested in pursuing clinical trials based on experimental models, and researchers interested in this arena would benefit from this text. There is little in this book that is relevant to the neuro-ophthalmologist, except for the chapter regarding mechanisms of oral tolerance, which deals with the human and experimental data on multiple sclerosis and autoimmune encephalitis.

Critical appraisal: This book fulfills its goal of summarizing the anatomy and immunology of the mucosal immune systems, with emphasis on the ocular mucosa. However, because it fails to include more clinical experience and information, it does not make this information relevant to the majority of ophthalmologists.

Alan G. Palestine, MD
Washington, DC

The Autonomic Nervous System and Its Effectors,  

Scope: This is a single-authored, hardcover book that serves as an introduction to the autonomic nervous system and its basic science. It reviews the anatomy, physiology, and chemistry of the autonomic nervous system from the perspective of a scientist, rather than that of a clinician. The author ends with focused reviews of the cardiovascular, gastrointestinal, and urogenital systems.

Contents: The book is organized into 10 chapters. After a historical introduction, the second chapter reviews the anatomy of the autonomic nervous system. The electrical properties of neurons, and neuromuscular and synaptic transmission are covered in two chapters. The basic pharmacology and chemistry are covered in three

chapters. The final three chapters review the cardiovascular and respiratory systems, the gastrointestinal system, and the renal, urinary, and reproductive systems.

Strengths: The writing is lucid, and the progression of chapters logical. The illustrations and reproductions are excellent. The tables complement the text nicely. In several chapters, the author uses boxes as expanded footnotes to review topics indirectly related to the chapter, such as a review of nerve fibers in the anatomy chapter, and a review of ionic distribution, action potentials, and voltage clamp technique in the electrical properties chapter. These boxes allow readers who are familiar with these topics or those less interested in them to omit them.

Deficiencies: The discussion in some chapters is quite laborious. For instance, the chapters on electrical properties and neuromuscular and synaptic transmission are overly detailed. The book also emphasizes physiology at the expense of chemistry and pharmacology. The autonomic control of pupil and sweat glands are, disappointingly, not covered.

Recommended audience: Graduate students, researchers, and clinicians beginning to think about the autonomic nervous system and its clinical import.

Critical appraisal: This is a very fine text that will serve as a complement to others dealing with the autonomic nervous system. It is probably less useful to clinicians who wish to seek answers for their patients with autonomic disorders, and is of limited use to the neuroophthalmic community.

Saifwan Jaradeh, MD
Professor, Department of Neurology
Medical College of Wisconsin
Madison, Wisconsin
Reorganization at NANOS

The North American Neuro-Ophthalmology Society (NANOS) is a professional organization composed of more than 400 ophthalmologists and neurologists. Its mission is to promote education, research, clinical expertise, and cordial exchange in the field of neuro-ophthalmology. To accomplish this mission more effectively, NANOS has recently made the following organizational changes:

1. Hired a management company, Association Resources, Inc., to guide the organization. The new NANOS Executive Office is now located at 342 North Main Street, West Hartford, CT 06117–2507. The Administrative Director is M. Suzanne C. Berry (sberry@nanosweb.org) and the Associate Director is Cheryl-Ann Tubby (ctubby@nanosweb.org).

2. Combined the annual NANOS and Frank B. Walsh meetings into one joint annual meeting (first meeting, February 10–14, 2002, in Copper Mountain, Colorado).

3. Altered the NANOS governing structure to include the following committees:
   a. Archives Committee (headed by Tom Carlow) to catalog NANOS and other neuro-ophthalmic artifacts for posterity.
   b. By-Laws Committee (headed by Shelley Cross) to review and revise the NANOS bylaws as recommended by the membership or Board.
   c. Communications Committee (headed by Preston Calvert) to update the NANOS Web site and e-mail communication lines, NANOSNET and NANOSLTR. (NANOSNET is the main e-mail method of communicating clinical issues among NANOS members and other interested physicians. NANOSLTR is the e-mail mechanism by which the Board and the Executive Office communicate administrative issues with the NANOS members.)
d. Education Committee (headed by NANOS President-elect Kathleen Digre), which is divided into subcommittees, to arrange courses and symposia at the American Academy of Ophthalmology Annual Meeting, to review abstracts submitted to the annual NANOS meeting, to oversee continuing education, to organize the annual NANOS meeting program, to formulate a curriculum for neuro-ophthalmology fellowship training programs, to put forward recommendations for medical student neuro-ophthalmology teaching programs, to develop outreach educational activities within the United States, and to initiate Internet-based educational opportunities for members, fellows, practitioners, and medical students.

e. Finance and Audit Committee (headed by the NANOS Treasurer Ralph Sawyer) to review budgetary
Robert McFadzean, MD, NANOS International Relations Committee.

Nancy Newman, MD, NANOS Publications Committee.

Laura Balcer, MD, NANOS Membership Committee.

Jack Selhorst, MD, NANOS Nominations Committee.

Mark Kupersmith, MD, NANOS Research Committee.

material with the management company and authorize payments outside the budget guidelines. The Development subcommittee (headed by Andrew Lee) is charged with obtaining grants and donations from individuals and companies interesting in sponsoring NANOS activities.

f. International Relations Committee (headed by Robert McFadzean) to develop an international associate program for foreign physicians unable to attend the NANOS meetings. Physicians in this program will have access to NANOSNET and much of the educational material on the NANOS Web site.

g. Membership Committee (headed by Laura Balcer) to review criteria for membership in NANOS and to determine whether applicants for membership meet those criteria. This committee also searches for ways to increase NANOS membership, promote interactions between junior
and senior NANOS members, and assist in the professional development of junior NANOS members.

h. Nominations Committee (headed by the NANOS Board Chair Jack Selhorst) to develop, with input from the membership, the slate of officers for yearly elections to the NANOS Board.

i. Publications Committee (headed by Nancy Newman) to interact with the editor and staff of the *Journal of Neuro-Ophthalmology* to ensure optimal running of the Journal.

j. Research Committee (headed by Mark Kupersmith) to coordinate and foster research related to neuro-ophthalmology among NANOS members, and to select the recipient of the NANOS Young Investigator Award, an award given to the best scientific presenter at the annual NANOS meeting.

k. Ad Hoc Committee on Certification, Accreditation, and Fellowship (headed by John Keltner) to keep members abreast of activities related to plans for accreditation of neuro-ophthalmology training programs and certification of neuro-ophthalmologists. Should NANOS members ask that NANOS take on the role of a certifying body, this committee would develop its mechanism.

l. Ad Hoc Practice Management Committee (headed by Richard [Skip] Legge) to update members on issues of clinical practice management.

m. Ad Hoc Committee of Women in Neuro-Ophthalmology (headed by Jacqueline Leavitt and Marian Rubenfeld) to address issues specific to women practicing or planning to practice neuro-ophthalmology.

We anticipate further changes and invite readers interested in learning more about NANOS to visit our Web site at http://www.nanos.org.
Calendar

Here are some upcoming meetings (through May 2002) of interest to neuro-ophthalmologists:

Feb. 9–14, 2002
Frank B. Walsh and North American Neuro-Ophthalmology Society (NANOS) Meeting
Copper Mountain Resort
Copper Mountain, CO
http://www.nanosweb.org/meetings/
Contact: (800) 856-9220

April 21–26, 2002
29th International Congress of Ophthalmology
Sydney, Australia
www.ophthalmology.aust.com
Contact: +61 2 9241 1478

May 5–10, 2002
The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Greater Fort Lauderdale/Broward County Convention Center
Fort Lauderdale, FL
http://www.arvo.org/meetgrid.htm
Contact: (240) 221-2900

May 5–8, 2002
International Neuro-Ophthalmology Society
Sheraton Buenos Aires Hotel & Convention Center
Buenos Aires, Argentina
Contact: inos2002@congresosint.com.ar

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Jeff Brown
Manager, Periodical Operations
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