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Diffusion Tensor Imaging and Tractography: Have They Come of Age?

Pia C. Sundgren, MD, PhD

In this issue of the Journal of Neuro-Ophthalmology, Lanyon et al (1) have demonstrated that the V5/medial temporal (MT) complex defined by functional MRI can be activated by direct thalamic or collicular input without involving V1 (primary visual, calcarine, or striate cortex). The authors have shown this connection by means of diffusion tensor imaging (DTI) and tractography. Although interesting and supported by previous findings in animals, their findings are dependent on imaging methodology that produces beautiful pictures but has substantial technical limitations.

DTI is an MRI-based methodology originally described in 1994 by Basser et al (2) that has become widely used in clinical practice and in brain research. DTI allows direct in vivo examination of some aspects of tissue microstructure and yields quantitative measures reflecting the integrity of white matter fiber tracts by taking advantage of the intrinsic properties of directionality of water diffusion in human brain tissue.

The diffusion of water molecules is characterized by Brownian motion. When water molecules are unconstrained, the direction of motion of a given molecule is random. The displacements of water molecules over time are described by a Gaussian distribution. The diffusion is called isotropic when the motion is equal and unconstrained in all directions. However, the microstructure of brain tissue forms physical boundaries that limit the Brownian motion of water molecules, resulting in a restriction of the total amount of diffusion. In microstructures such as the white matter fibers, the diffusion of water molecules will be relatively more restricted in a direction perpendicular to the microstructural boundaries than parallel to them. Such diffusion is termed “anisotropic.”

Anisotropic diffusion is characterized not by a single coefficient, but by a second-order symmetric tensor of six unique elements or diffusivities requiring multiple measurements for complete determination. Once these six diffusion coefficients have been obtained, the degree of mobility of water protons in the system can be determined with an average principal diffusivity. The degree of anisotropy of this mobility can be found by calculating anisotropy indices such as fractional anisotropy (FA). FA is a measure of the portion of the magnitude of the diffusion tensor due to anisotropy and gives information about tissue organization, degree of myelination, and water mobility. The most widely used measure of anisotropy in the DTI literature, FA has a value that varies from zero, in the case of isotropic diffusion, to a maximum of 1, indicating perfectly linear diffusion occurring only along the primary eigenvector. The information can be presented in two dimensions by a widely accepted color scheme originally proposed by Pajevic and Pierpaoli in 1999 (3). It incorporates the anisotropy and directional information and attributes a specific color to each of the different orientations of the axonal fibers.
Almost a decade ago, several research groups began to use the three-dimensional (3D) information present in DTI to create 3D virtual trajectories in a method called “tractography.” The objective of DTI fiber tracking is to determine intervoxel connectivity on the basis of the anisotropic diffusion of water. In tractography, the local fiber orientation in each voxel is determined via DTI. Voxels are then connected to each other, starting at a seed point and propagating a tract by mathematically connecting the adjacent voxels based on information gleaned from the magnitude and directionality of diffusion anisotropy.

Hundreds of tractography studies of white matter connectivity have now been performed in healthy and diseased brain. The technique has become a particularly useful clinical tool in presurgical planning. It provides information about whether white matter tracts adjacent to a brain tumor are merely displaced or invaded (Fig. 1). DTI and tractography have also been popular in anatomic connectivity studies of healthy and diseased individuals and in the assessment of the immature brain in neonates, congenital brain malformations, demyelinating diseases, and epilepsy. For example, DTI and fiber-tracking studies have demonstrated abnormal white matter tracts within the cerebellum and cerebrum in holoprosencephaly that were not apparent on conventional MRI. DTI may prove invaluable in identifying potential epileptogenic foci as well as more optimally defining the extent of the lesion proposed for surgical resection.

There are several limitations to DTI and tractography. Background noise, patient movement, and distortion from imaging artifacts produce uncertainty. Accuracy of the constructed fiber tract is limited by the information contained in the diffusion tensor and in the different methods of constructing the tracts. DTI tractography cannot distinguish antegrade from retrograde information flow along a fiber pathway. Another limitation is the assumption that diffusion has Gaussian characteristics, which is not correct when diffusion is restricted. There is even experimental evidence that diffusion in normal white matter is non-Gaussian at high b-values (which represent the overall diffusion in an experiment). Even if the problems with non-Gaussian diffusion are solved, there is as yet no clinically applicable method of modeling non-Gaussian diffusion.

An important user limitation of DTI/tractography is that when selecting a specific fiber system, one has to know beforehand the anatomy of the white matter tracts. Furthermore, tractography is a mathematical estimation of white matter tracts rather than an anatomic depiction. Axonal fibers can appear disproportionately large because of higher FA. Further research is needed to reduce or eliminate the confounding problem created by crossing fibers and partial volume effects. Spatial resolution must improve to allow visualization of small fiber tracts.

Because these colorful images of the white matter bundles are so beautiful, it is easy to be swayed. Before doing so, we will need better methods to deal with non-Gaussian diffusion, crossing fibers, and partial volume effects. Only then will DTI and tractography provide robust and clinically useful information.
To learn more about the utility, limitations, and promise of DTI and tractography, consult excellent current reviews by Mori and van Zijl (4) and Mukherjee et al (5,6).

REFERENCES
Combined Functional MRI and Diffusion Tensor Imaging Analysis of Visual Motion Pathways

Linda J. Lanyon, PhD, Deborah Giaschi, PhD, Simon Au Young, MSc, Kevin Fitzpatrick, BSc, Lu Diao, Bruce H. Bjornson, MD, and Jason J. S. Barton, MD, PhD

Background: Motion perception may be preserved after damage to striate cortex (primary visual cortex, area V1). Awareness and normal discrimination of fast-moving stimuli have been observed even in the complete absence of V1. These facts suggest that motion-sensitive cortex (the V5/MT complex or V5/MT+) may be activated by direct thalamic or collicular inputs that bypass V1. Such projections have been identified previously in monkeys but have not been shown in humans using neuroimaging techniques.

Methods: We used diffusion tensor imaging (DTI) tractography to visualize white matter fiber tracts connecting with V5/MT+ in 10 healthy volunteers. V5/MT+ was localized for each subject using functional MRI (fMRI). Functional activity maps were overlaid on high-resolution anatomical images and registered with the diffusion-weighted images to define V5/MT+ as the region of interest (ROI) for DTI tractography analysis. Fibers connecting to V1 were excluded from the analysis.

Results: Using conservative tractography parameters, we found connections between the V5/MT+ region and the posterior thalamus and/or superior colliculus in 4 of 10 subjects.

Conclusions: Connections between the V5/MT+ region and the posterior thalamus and/or superior colliculus may explain visual motion awareness in the absence of a functioning V1.

In this study, we used neuroimaging techniques to investigate the presence of subcortical connections to V5/MT+ in healthy human subjects. We first used functional magnetic resonance imaging (fMRI) to localize V5/MT+ in each subject because the exact anatomical location of this area is subject to individual variation (28,29). Diffusion tensor imaging (DTI) tractography was then used to image potential fiber tracts emanating from the V5/MT+ region of interest (ROI) that did not involve V1. This combined fMRI/DTI analysis allowed us to determine whether there were any tracts traveling between V5/MT+ and the thalamus and midbrain.

METHODS

Subjects

Ten healthy volunteers (4 men and 6 women, aged 20–37 years) participated in this experiment. The protocol was approved by the institutional review boards of Vancouver General Hospital and the University of British Columbia, and all subjects gave informed consent in accordance with the Declaration of Helsinki.

Apparatus and Procedure

Scans were conducted on a Phillips 3-T magnetic resonance scanner at the University of British Columbia High Field MRI Centre. The scanning session consisted of a T1 high-resolution structural scan (magnetization prepared rapid acquisition gradient echo [MPRAGE] with sensitivity encoding [SENSE]; time to recovery [TR] ~10 msec, time to echo [TE] 6 msec, field of view 212 x 212 mm, slice thickness 1.1 mm, 256 x 256 reconstruction matrix, voxel size 1.1 x 1.1 mm, and reconstructed voxel size 0.83 x 0.83 mm), a T2* fMRI scan using echo planar imaging (SENSE; TR 2000 ms, TE 30 msec, field of view 240 x 240 mm, 36 interleaved axial slices of 3-mm thickness with 1-mm gap, 80 x 80 matrix, 128 x 128 reconstruction matrix, voxel size 3 x 3 mm, and reconstructed voxel size 1.88 x 1.88 mm), and three consecutive diffusion-weighted scans using 32 diffusion sensitizing directions (SENSE; TR ranging from 5586 to 6307 msec, TE 69 msec, B value 700 s/mm², field of view 212 x 212 mm, 56–60 axial slices of 2.2-mm thickness, no gap, 96 x 96 matrix, 256 x 256 reconstructed matrix, voxel size 2.21 x 2.21 mm, and reconstructed voxel size 0.83 x 0.83 mm).

The purpose of the functional scan was to localize the region of the cortex sensitive to motion for each subject because there are large individual differences in the exact location of this region (28,29). Subjects fixated the center of a display containing white dots, each of 20-minute size (0.3°, 5 X 5 pixels), at 2% density on a black background. The dots moved radially in and out from the center of the pattern for 14 seconds at a speed of 7.5 per second and then remained stationary for 14 seconds. This process was repeated for six cycles.

DTI and fMRI Analysis

We used DTI tractography techniques to probe white matter tract topology ((30); for reviews see (31,32)). Although DTI studies commonly refer to “white matter” topology, unmyelinated axonal membranes also lead to anisotropic diffusion (33). However, myelin is thought to modulate the degree of anisotropy (34). For each individual subject, we used DTI Studio version 2.40 software (Hiang and Mori, http://lbam.med.jhmi.edu/dtiuser/dtiuser.asp) to perform streamlined fiber tracking, based on the fiber assignment by the continuous tracking method (FACT) (35) for the whole brain. The gradient directions used during the scan were corrected for individual subjects’ head positions using program code provided by the Kennedy Krieger Institute (http://godzilla.kennedykrieger.org/~jfarrell/software_web.htm), recommended for use with DTI Studio. Whole brain tractography was performed such that fiber tracking was started at voxels with a fractional anisotropy (FA) value greater than 0.2 and ended when a voxel was encountered with an FA value less than 0.2. A threshold of 0.2 is commonly used for this type of deterministic tractography (for example, (36)) because FA values less than 0.2 tend to be found in grey matter, whereas values

FIG. 1. Regions of interest (ROIs) of V5/MT+ based on functional activity (arrows). As is normal for visual motion tasks, functional activity is also present in posterior occipital cortex (arrowheads) because activity in this region is above the threshold used to identify V5/MT+ activity. The posterior occipital activity is not used for DTI analysis. L, left; R, right.
greater than 0.2 are found in white matter (37). The maximum turning angle (the angle over which neighboring tensor principal vectors are joined to form a tract) was set to 45. Both of these parameters are in the middle of the range recommended for DTI Studio.

To confirm the reliability of the whole brain tractography in each subject, we identified the optic radiation and corpus callosum white matter tracts resulting from the tractography.

Functional activity was analyzed using Brain Voyager QX versions 1.7 and 1.8 (Brain Innovation, www.brainvoyager.com). Activity in the moving versus the stationary dot conditions was compared using a general linear model, and areas of peak activity for motion were determined using a threshold of \( q < 0.001 \). Only regions containing a cluster of at least 50 consecutive significantly activated voxels were accepted. The functional data were overlaid on the high-resolution anatomic images (obtained from the T1 structural scans), and the resulting images were registered with the diffusion images for analysis in DTI Studio. In DTI Studio, the ROI for tractography was drawn manually on the basis of the location of V5/MT+ functional activity (Fig. 1). V5/MT+ is located very close to fibers of the optic radiation, and, therefore, our ROI drawing was particularly conservative in that region. The posterior occipital region was specifically excluded from the ROI using the drawing tool “NOT” function so that fibers traveling to V1 were removed from analysis. Fibers connected to the V5/MT+ ROI were then analyzed by visual inspection to determine the number that connected with the posterior thalamus and/or superior colliculus, which were identified based on anatomical landmarks from a detailed MRI atlas (38). For larger fiber bundles, the statistics feature of DTI Studio was used to count fibers when individual fibers could not be determined visually. As a control, we performed a second analysis in which we drew an ROI deep in the intraparietal sulcus (IPS).

Our analysis was performed at an individual level because the functional localizer, on which tractography was based, gave the specific location of V5/MT+ for each subject. The fiber analysis provided information about

FIG. 2. All fibers tracked from V5/MT+ for Case 3. The slice views focus on the pulvinar nucleus. The top left panel shows a rotation-enabled three-dimensional view of the fibers against a semitransparent two-dimensional axial slice. The top right panel shows an axial slice view, and the bottom row shows sagittal and coronal slice views. Each slice view contains only those fibers present in that particular slice, with fibers being randomly colored for visualization purposes. V5/MT+ functional activation was not present in the left hemisphere for this subject. From the right hemisphere V5/MT+, several fibers were tracked to the pulvinar.
fibers traveling to and from this location in each individual and revealed individual variation in results.

RESULTS

We found direct connections between V5/MT+ and subcortical locations in 4 of our 10 subjects (Table 1; Figs. 2 through 5). All 4 of these subjects (Cases 1-4) had fibers connecting V5/MT+ with the pulvinar nucleus. Two subjects (Cases 1 and 4) had fibers connecting with the superior colliculus. One subject (Case 4) had fibers connecting with the region of the LGN. An example of the tractography results in Case 6, typical of the remaining subjects, is shown in Fig. 6. We do not believe the difference in tractography results is due to an age-related effect in the diffusion data because the 4 subjects in whom connections were found included the oldest subject (age 37) and 2 of the youngest subjects (age 22). From the control analysis, none of the subjects had fibers extending from our IPS ROI to the thalamus, superior colliculus, or LGN.

Fibers to the right pulvinar nucleus were numerous in Case 3. This could be because visual motion-related activation was unilateral (it was bilateral in our other subjects), and this pathway might be preferentially strengthened in this hemisphere in this individual. However, any quantitative comparison of DTI reconstructive tracts is made with caution because the results relate to lines propagated through the tensor map rather than to numbers of real fibers.

In 3 of these 4 subjects, we also found fibers that extended inferiorly in the brainstem through the pons and a small number that proceeded into the medulla. Feedback connections from V5/MT+ to the pons are known to exist in monkeys (23,39). A few of the pontine fibers continued to be tracked through the middle cerebellar peduncle to the cerebellum, but the extensively crossing fibers present in the pons increase the likelihood of tractography artefacts in this case.

To establish whether this individual variation in our results was due to differences in the size of the region of functional activation, we performed a further control set of analyses. We identified the ROI for tractography using a large oval around but extending beyond the region of functional activity in the subjects for whom we did not find fibers to the thalamus. This analysis revealed fibers to the thalamus (pulvinar) in only one additional subject. We performed a further set of tractography analyses for this subject using ROIs systematically extending in size in different directions. These analyses revealed that the

![FIG. 3. Fibers tracked from V5/MT+ for Case 3 to the medial pulvinar nucleus only. Fibers are shown in 3 dimensions against a two-dimensional axial slice.](image)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Superior Colliculus</th>
<th>Pulvinar</th>
<th>LGN</th>
<th>Cerebellum or Cerebellar Peduncles</th>
<th>Brain Stem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td></td>
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<td>2</td>
<td>37</td>
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<td>3</td>
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<td>0</td>
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</tr>
<tr>
<td>4</td>
<td>25</td>
<td>6</td>
<td>19</td>
<td>4</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

++, large bundle of fibers.

*The number of reconstructed tracts is shown. Note that a quantitative analysis is not appropriate in relation to DTI reconstructed tracts. Numbers of fibers relate to the lines of tractography that have propagated through the tensor map and do not express the number of real fiber tracts.
FIG. 4. All fibers tracked from V5/MT+ for Case 4. Tractography in this subject revealed numerous V5/MT+ fibers connecting with the superior colliculus, pulvinar nucleus, and LGN, as well as the pons and cerebellum. The slice views focus on the fibers tracked to the vicinity of the LGN in the right hemisphere. This region is highlighted with a black oval on the axial and coronal views.

FIG. 5. All fibers tracked from V5/MT+ for Case 4. Tractography in this subject revealed numerous V5/MT+ fibers connecting with the superior colliculus, pulvinar nucleus, and LGN, as well as the pons and cerebellum. The slice views focus on the fibers tracked to the vicinity of the LGN in the right hemisphere. This region is highlighted with a black oval on the axial and coronal views.

pulvinar fibers resulted from extending the ROI medially far beyond the functionally defined region into the neighboring white matter of the optic radiation in one particular slice. Extending the ROI in other directions and by lesser amounts did not produce fibers. Therefore, we consider this result to be due to fibers of the optic radiation from V1 and conclude that this subject, like the other remaining 5 subjects, does not have fibers tracking directly between V5/MT+ and the thalamus.

DISCUSSION

Our study used fMRI to identify the V5/MT+ regions in each subject and then used DTI to visualize fiber tracts projecting between V5/MT+ (but not V1) and other structures, in particular the posterior thalamus and superior colliculus. Given the proximity of the optic radiations to V5/MT+, we identified the V5/MT+ region conservatively, as well as excluding any fibers that projected to posterior occipital cortex. With this conservative approach, our DTI data suggested the presence of tracts linking V5/MT+ with the pulvinar nucleus and the LGN in the posterior thalamus and the superior colliculus in 4 of 10 subjects.

A recent DTI investigation (40) also showed connections between the pulvinar and the V5/MT+ region by tracking fibers from the pulvinar as the ROI, but V5/MT+ was not localized by fMRI in that study.

It has been suggested that a direct connection to V5/MT+ from the superior colliculus, pulvinar nucleus, or LGN could mediate residual visual motion perception in the absence of V1 (22). In monkeys, MST and FST are reciprocally connected to the pulvinar and project to the pons (23). Feedback connections have been found from MT to the pulvinar nucleus, LGN, superior colliculus, and pons in the macaque monkey (39) and the prosimian primate Galago senegalensis (41). More relevant for the issue of residual vision and blindsight are feed-forward thalamic and collicular projections to V5/MT+ in monkeys that have also been described (21–27). In squirrel (24) and rhesus (26) monkeys, the pulvinar projects to the MT. The MT is the major cortical target of the medial nucleus of the inferior pulvinar in owl monkeys (25).
We found fibers connecting V5/MT+ to the vicinity of the superior colliculus in 2 of our 10 subjects. Lesions of the superior colliculus alone have little effect on medial temporal responses in macaque monkeys, but combining collicular lesions with V1 lesions renders the MT visually unresponsive (42). This information suggests that the superior colliculus may be a key source of input in the absence of V1, either through direct projections to extrastriate cortex or via a relay in the pulvinar. Another DTI study (43) reported extensive projections between the superior colliculus and visual cortical areas in two hemispherectomized patients with residual motion perception but limited projections in hemispherectomized patients with no conscious awareness of vision.

Our results confirm a similar variability in the projections between V5/MT+ and subcortical regions in normal subjects. It should be noted that the technical limitations of DTI tractography can produce some variability, particularly when tracking through regions of complex fiber structure. However, the diversity in our results could also reflect a true intersubject variability of pathways, as suggested by others (43). Variability in the viability of projections from subcortical structures to V5/MT+ may explain why only some patients with V1 lesions have residual motion perception or blindsight. Large group studies suggest that only a minority of patients with cortical visual loss have residual abilities (44–46). Although there are many potential factors that could contribute to this variability, such as the extent of training, age at onset (2,47–49), and degree of additional damage to the extrastriate cortex (2,47–51), variations in the pre-morbid anatomy of pathways between the superior colliculus/pulvinar nucleus and the V5/MT+ region may be another important factor. The fact that we found such pathways in a minority of healthy subjects is consistent with the finding that only a minority of patients with cortical visual loss have blindsight.

We stress that our DTI analyses cannot provide definitive proof of these projections, inasmuch as the technique cannot tell us whether these projections are from subcortical structures to V5/MT+, from V5/MT+ to subcortical structures, or both. The data from monkey studies suggest that there are feed-forward and feedback pathways connecting these structures, but DTI cannot provide data on the direction of information flow. Rather, these results can only be viewed as consistent with suggestions that, if visual information can be transmitted directly from subcortical
regions to V5/MT+ without mediation by V1, such tracts should exist. Further work showing whether the presence of these tracts correlates with residual visual perception would be an important step in verifying the role of these tracts in vision.

Acknowledgments

We thank our subjects for their time in participating in the experiment. We also extend grateful thanks to Natasha Pollock and Nailyn Rasool for participating in parts of the tractography analysis, and to George Malcolm and Robert Orlando, who participated in early stages of the project. Thanks go to staff, especially Trudy Harris, at the University of British Columbia High Field MRI Centre, and to Burkhard Maedler of Phillips Medical Systems for his helpful advice.

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Absence of Neuromyelitis Optica IgG Antibody in an Active Relapsing-Remitting Multiple Sclerosis Population

Craig H. Smith, MD, Emmanuelle Waubant, MD, PhD, and Annette Langer-Gould, MD, PhD

Background: Neuromyelitis optica (NMO, Devic disease) had been defined clinically until a novel autoantibody directed against the aquaporin-4 channel (NMO IgG antibody) was identified. Although previous studies have demonstrated that the NMO IgG antibody is not present in patients with multiple sclerosis (MS), these studies may have been biased by the inclusion of patients with inactive MS. We resolved to test for NMO antibody in a population of patients with active relapsing-remitting (RR) MS.

Methods: A total of 130 patients with RRMS previously enrolled in phase I \((n = 26)\) and phase II \((n = 104)\) trials of rituximab therapy were tested for serum NMO IgG antibody at the Mayo Clinic Neuroimmunology Laboratory by indirect immunofluorescence on a substrate of mouse central nervous system tissue. Serum samples were obtained at baseline before initiation of therapy. All patients had experienced at least one relapse in the year before study entry and had not received treatment with immunomodulatory agents for at least 2 months.

Results: None of the 130 patients with active RRMS tested positive for NMO IgG antibody.

Conclusions: Our findings indicate that anti-aquaporin-4 immunoreactivity is unlikely to play a role in the pathogenesis of RRMS and support the results of previous studies suggesting that the NMO IgG antibody is specific for NMO. Similar studies in a larger cohort will be necessary to fortify our conclusions.


Neuromyelitis optica (NMO, Devic syndrome) is an inflammatory demyelinating disease that predominantly affects the optic nerves and spinal cord (1-4). NMO is rare and is frequently misdiagnosed as multiple sclerosis (MS), although it differs from MS in prognosis and response to treatment (3,5-9). Its distinct neuropathologic features, radiologic pattern, and fulminant clinical course suggest that it is a distinct disease (4,10). Indeed, a novel auto-antibody directed against the aquaporin-4 channel (NMO IgG antibody) was recently identified as a potential NMO diagnostic test (10,11). Although previous studies have demonstrated a high specificity of the NMO IgG antibody for NMO, these studies may have been biased by the inclusion of patients with MS with inactive disease. If the presence of NMO IgG antibody were an epiphenomenon of central nervous system (CNS) inflammation, some individuals with active relapsing MS might also test positively for the antibody.

To further validate the specificity of the NMO IgG antibody, we have tested for its presence in a cohort of 130 patients with active relapsing-remitting (RR) MS previously enrolled in two clinical trials. We have also explored whether the clinical diagnosis of NMO is adequate in excluding such patients from clinical trials of RRMS.

METHODS

Sera from 130 patients with RRMS, as defined by MacDonald criteria 1-4 (12), who were previously enrolled in phase I \((n = 26)\) and phase II \((n = 104)\) clinical trials were retrospectively tested for NMO IgG antibody. These trials were designed to evaluate the safety and efficacy of the anti-CD20 antibody rituximab in treating patients with active RRMS.

Serum samples were obtained before rituximab therapy was initiated. Patients had experienced at least one relapse in the year before study entry and had not received treatment with immunomodulatory agents such as interferon and glatiramer acetate for at least 2 months. Exclusion criteria included NMO defined solely by clinical judgment according to published criteria (15).

NMO IgG antibody was assayed in a masked fashion at the Mayo Clinic Neuroimmunology Laboratory by indirect immunofluorescence on a substrate of mouse central nervous system tissue (11).
RESULTS

Patient characteristics in phase I and phase II trials are provided in Table 1. Clinical characteristics of previous exacerbations were not available for review. None of the 130 patients with active RRMS tested positive for NMO IgG antibody.

DISCUSSION

We found that in two active RRMS populations previously enrolled in clinical trials, anti-aquaporin-4 immunoreactivity was undetectable in serum. It is thus unlikely that this antibody plays a role in the pathogenesis of RRMS or is an epiphenomenon of MS disease activity.

Multiple independent investigations have shown a wide range of sensitivity (58%-73%) but a high specificity (>90%) of the NMO IgG antibody for the diagnosis of NMO (2,15). Our results further confirm its high specificity and therefore support the notion that NMO is a distinct entity and suggest that relying on clinical judgment to exclude patients with NMO from RRMS clinical trials appears to be valid.

The revised 2006 diagnostic criteria for NMO (15) remove the stipulation that NMO be limited to the optic nerves and spinal cord and emphasize NMO IgG seropositivity and the specificity of longitudinally extensive spinal cord lesions. Traditionally considered a severe variant of MS, NMO appears to be easily distinguishable when the defining criteria include the presence of this autoantibody. As disease-modifying treatments for NMO may be different from those for MS, early recognition of NMO is important for prevention of serious neurologic deficits (5-9).

<table>
<thead>
<tr>
<th>TABLE 1. Demographic characteristics of patients in phase I and phase II trials of rituximab in the treatment of relapsing-remitting multiple sclerosis (2,3)</th>
</tr>
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<tbody>
<tr>
<td><strong>Phase I Study</strong></td>
</tr>
<tr>
<td>Number enrolled</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Female (%)</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>White (%)</td>
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<tr>
<td>Black (%)</td>
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<tr>
<td>Hispanic (%)</td>
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<tr>
<td>Other (%)</td>
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<tr>
<td>Disease duration (years)</td>
</tr>
<tr>
<td>Since onset</td>
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<tr>
<td>Since diagnosis</td>
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<tr>
<td>EDSS score</td>
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<tr>
<td>0</td>
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<tr>
<td>1.0–1.5</td>
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<tr>
<td>3.0–3.5</td>
</tr>
<tr>
<td>4.0–4.5</td>
</tr>
<tr>
<td>5.0</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
</tr>
<tr>
<td>Relapses in past year</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td>Mean (minimum, maximum)</td>
</tr>
</tbody>
</table>

Data are mean SD or n (%) unless specified otherwise. EDSS, Expanded Disability Status Scale.
Confirming the differences between MS and NMO also has implications for designing and interpreting randomized controlled trials (15,16).

This is the first report of an NMO IgG antibody assay in patients in an MS clinical trial. Considering that diagnosis of NMO is relatively infrequent (0.3%) in patients with clinically isolated syndromes suggestive of MS (17), we were unlikely to detect NMO antibody in our sample of only 130 patients. Our study thus has two main limitations. First, the small sample size decreases the chance of erroneous enrollment of NMO patients. Second, clinical characteristics of relapses were not available; thus, we are unable to comment on possible inclusion of opticospinal forms of MS. However, the Asians in our cohort represented less than 1% of the total population (Table 1). Larger, more well-defined RRMS cohorts will have to be studied before one can be more certain that NMO IgG is not an epiphenomenon of active demyelination.

Acknowledgments

Drs. Emmanuelle Waubant and Annette Langer-Gould had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We thank Dr. Christopher Dant of Genentech for his assistance in the preparation of this article.

REFERENCES


Bilateral Mesial Occipital Lobe Infarction After Cardiogenic Hypotension Induced by Electrical Shock

Roheena Kamyar, MD and Jonathan D. Trobe, MD

Abstract: A 28-year-old man developed cerebral blindness from infarction of both mesial occipital lobes after cardiogenic hypotension induced by electrical shock. He remained globally encephalopathic for several weeks, but his most enduring deficit was bilateral homonymous hemianopias with macular sparing. Cerebral visual loss after electrical injury has been sparsely reported. It has been attributed to direct thermal injury of the skull or posterior dural venous sinuses. We suggest that cerebral blindness after cardiogenic hypotension in which there is no thermal injury to the scalp be attributed to hypotensive infarction of the mesial occipital lobes, which lie in the terminal domain of the posterior cerebral arteries.


CASE REPORT

A 28-year-old male roofer sustained an electrical injury of 220 Volts alternating current (AC) while moving a large extension ladder with a coworker. He was on the ground securing the ladder on which his coworker was perched. The ladder pitched backwards and came into contact with overhead power lines. Conducted through the ladder, the electrical discharge immediately caused his coworker to be thrown to the ground. Our patient continued to grip the ladder for approximately 15 seconds before falling to the ground.

According to witnesses, he displayed tonic-clonic movements for several minutes and then “turned blue.” Bystander resuscitation began promptly and continued for approximately 6 minutes until emergency medical technicians arrived. At that point, cardiac monitors were positioned and the patient was found to be in pulseless ventricular tachycardia. He received three AC cardiac shock treatments and two rounds of epinephrine and atropine before he developed sinus rhythm. He was estimated to have been in cardiac arrest for approximately 10 minutes. After endotracheal intubation, he was brought to our emergency department where his Glasgow Coma Scale score was 3T. His pulse ranged from 120 to 140 and his blood pressure from 120 to 160 systolic to 80 to 90 diastolic. His temperature was 98.6°F, and pulse oximetry was 99% on room air with an endotracheal tube in place.

External injuries were limited to a 1-cm full-thickness skin burn over the medial left foot at the base of the first phalanx and a 3-cm full-thickness skin burn over the lateral right foot, considered to be exit wounds. He was placed under a cooling protocol for 48 hours, paralyzed with cisatracurium, and sedated with propofol and fentanyl.

On day 4, when sedation was discontinued he was agitated and unresponsive to voice or painful stimuli. Pupils were of normal size and reactivity. Deep tendon reflex examination evoked myoclonus. Tone was increased in the lower extremities. Plantar reflexes were extensor bilaterally.

Head and spine CT performed on day 1 and day 4 was normal. On day 5, brain MRI revealed hyperintense signal and parenchymal thickening (loss of gray-white distinction and sulcal narrowing) in the mesial occipital regions.
bilateral on T2, FLAIR, and diffusion sequences and hypointense signal in the corresponding regions on apparent diffusion coefficient maps (Fig. 1). There were no other unequivocal abnormalities. These findings suggested relatively selective ischemia of the mesial occipital lobes.

In the next 3 weeks, the patient’s agitation gradually dissipated, and he became more alert. Once able to communicate, he expressed an inability to see.

Our examination on day 25 disclosed that he was attentive and oriented to location but not to time. He could not recall what he had eaten earlier that day. Cranial nerve examination was normal except that he had only hand movement vision in both eyes. He had normal strength, tone, reflexes, and sensation in all extremities. We made a diagnosis of cardiogenic hypoxic-ischemic encephalopathy most prominently affecting the mesial occipital lobes.

By day 50, visual acuity had improved to 20/200 in each eye. Humphrey visual field examination showed severely constricted fields (Fig. 2) in a pattern suggestive of bilateral homonymous hemianopia with macular sparing. By day 76, visual acuity had improved to 20/30 in both eyes, but visual fields were unchanged. On informal mental status testing, he appeared to be intact.

DISCUSSION

Our patient developed bilateral homonymous hemianopias with macular sparing in the setting of electrical shock. Although other parts of the brain were clinically affected, the most enduring deficit was cerebral visual loss. The structural imaging abnormalities were strikingly limited to the mesial occipital region. We believe that the visual loss was not a direct result of current flow to the brain, but an indirect effect of cardiogenic hypotension caused by electrical effects on the cardiac conduction system.

Oddly, there has been only one report in which cardiogenic hypotension was documented before cerebral visual loss in the setting of electrical shock. Although other parts of the brain were clinically affected, the most enduring deficit was cerebral visual loss. The principal mediator of tissue damage in electrical injury is the conversion of electrical energy into heat. The amount of heat generated is dependent on the amount and duration of current flow and the amount of resistance encountered by the current in the various body tissues. As it searches for a grounding source, the electrical current typically takes the path of least resistance. Tissues with the least resistance include nerves and blood vessels. Tissues with greater resistance include muscle, skin, tendon, fat, and bone. When current exits the body, a significant amount of thermal damage may cause full-thickness skin burns, as occurred in our patient’s feet.

The familiar opthalmic manifestations of electrical injury are generally thought to be caused by the thermal effect of the electrical current passing through the eyes (6). The most commonly described ocular injuries are corneal burns (7), cataracts (8,9), subretinal macular hemorrhages (10), bilateral macular holes and cysts (11,12), and anterior ischemic optic neuropathy (6).

The mechanism of cerebral visual loss has received less attention. A logical mechanism of injury would be direct thermal injury to the skull or brain. Indeed, Tamler (1) reported a 36-year-old man shocked by a high-tension line carrying 12,000 V who had a right occipital region scalp burn and a congruous left homonymous hemianopia attributed to direct injury from the burn (1). This report antedated the availability of sophisticated brain imaging.

Patel and Lo (2) reported a 31-year-old man who was shocked when his right hand came into contact with a 15,000-V capacitor. Cerebral angiography disclosed cerebral thrombosis in the distal left vein of Labbe’, which caused right facial and arm numbness and weakness and a “right visual field defect.” No further clinical details were provided (2). The authors proposed that the venous thrombosis developed from vasospasm and intimal damage induced by the heating effect of electricity that traveled through brain vessels.

Gans and Glaser (4) reported a 53-year-old hypertensive man who was shocked in the left hand while working with a set of wires carrying 220 V of AC (4). He suffered no immediate deleterious effects, but awakened 4 days later with the inability to see objects in his right hemifield. CT revealed a hypodense lesion in the left occipital region consistent with a cortical infarct. Although the authors proposed a causal relationship between the occipital infarct and the electric injury, there is scant evidence to support that contention.

More pertinent to our case is the report of Perez-Molina et al (3), who described a 16-year-old boy who experienced an electrical injury while playing an electric guitar (3). He had a cardiopulmonary arrest and was resuscitated after 10 minutes. Upon awakening, he complained of an inability to see. FLAIR MRI the next day revealed hyperintense signal in both occipital lobes. There was no mention of a diffusion sequence. The MRI findings resolved after 20 days, as did the patient’s visual loss. Because of the reversibility of the patient’s condition, the authors attributed the injury to a direct electrical injury to the brain. They proposed the phenomenon of “electroporation” or alteration in the electrochemical balance between the intracellular and extracellular compartments because of the effect of electricity on cellular plasma membranes. This phenomenon can increase membrane porosity and result in an increase in extracellular edema. The authors attributed the transient blindness and MRI...
FIG. 1. Brain MRI performed on day 5 after the electrical shock episode. Axial sections through the medial occipital regions (left column) show high signal on the T2 (A) and diffusion (B) images and low signal on the corresponding apparent diffusion coefficient (ADC) map (C). The T2, diffusion, and ADC axial images in the parietal region (right column) are normal.
FIG. 2. Humphrey visual field examination on day 50 shows macular-sparing bilateral homonymous hemianopias.

abnormalities to vasogenic edema similar to that seen in posterior reversible encephalopathy syndrome (PRES). We suspect that the patient reported by Perez-Molina et al (3) experienced visual loss from the same mechanism as did our patient but in milder form.

Cardiopulmonary arrest is the most common cause of immediate death in electrical injury (13). If there is successful resuscitation after electrical injury, the patient’s outcome usually depends on whether hypoxic-ischemic encephalopathy develops. Although cardiopulmonary arrest is a common outcome of severe electrical injury, there is no previously reported link between cerebral visual loss and hypoxic-ischemic encephalopathy induced by electrical injury. It is possible that this connection has been overlooked because clinicians and radiologists expect systemic hypotension to cause infarction in the “watershed” domain that lies between the major cerebral arteries. The watershed domain in the posterior brain hemispheres is classically in the parieto-occipital region rather than in the mesial occipital region, the area affected in our patient. The clinical correlate of parieto-occipital ischemia is Balint-Holmes syndrome, in which patients typically have visual spatial, attentional, and ocular motor deficits with sparing of visual acuity and visual fields (14). However, several reports have documented that the epicenter of cerebral damage in systemic hypotension may be the mesial occipital region or primary visual cortex (15). The clinical correlate of mesial occipital damage is bilateral homonymous hemianopia, often with macular sparing, as our patient demonstrated. The macular sparing that often accompanies bilateral homonymous hemianopias in such cases has been attributed to the fact that the occipital polar region that serves central (“macular”) vision receives a dual blood supply, being served by both the posterior and middle cerebral arteries (14,15).

REFERENCES

A Case of Acute Posterior Multifocal Placoid Pigment Epitheliopathy With Recurrent Stroke

Katie Luneau, MD, Nancy J. Newman, MD, Sunil Srivastava, MD, and Valerie Biousse, MD

Abstract: A 43-year-old man who had visual loss from acute posterior multifocal placoid pigment epitheliopathy (APMPPE) developed a right middle cerebral artery territory infarction a few weeks after the visual loss occurred and shortly after corticosteroid therapy was tapered. He was then treated continuously with oral low-dose prednisone and cyclophosphamide but presented with recurrent cerebral infarction 6 months later, shortly after cyclophosphamide was replaced with azathioprine. Neurologic complications of APMPPE are exceedingly rare, with only 18 other well-documented cases of APMPPE in the English and French literature. Cerebral vasculitis was the presumed mechanism in most patients, but only 2 patients had pathologic confirmation. There have been only 3 reported cases of recurrent cerebral infarction, all occurring during corticosteroid taper. Because neurologic complications of APMPPE are rare, it is reasonable to reserve neuroimaging for patients who have unusual headaches or other new neurologic manifestations.


A acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is characterized by ophthalmic manifestations consisting of multifocal cream-colored placoid lesions at the level of the choroid (1,2). It usually affects both eyes, men and women equally, and mostly young adults (2). Patients typically present with isolated decreased visual acuity. The fundus lesions generally resolve spontaneously over a few weeks, leaving alterations in the pigment epithelium. Fluorescein angiography demonstrates characteristic hypofluorescent lesions in the early phase of the angiogram ("block early") followed by hyperfluorescence ("stain late") (1,2). The visual prognosis is usually good, often with spontaneous visual recovery without treatment. Systemic corticosteroids are sometimes used in treatment but without proven efficacy (1-26).

APMPPE rarely includes cerebral vasculopathy, usually manifesting as stroke. Only 18 patients with cerebral vasculopathy have been described in the English and French literature (2-13). We report a patient with APMPPE who had two cerebral infarctions, the first occurring within weeks of onset of the ophthalmic manifestations, shortly after corticosteroid treatment was tapered, and the second occurring 6 months later, when cyclophosphamide treatment was replaced with azathioprine treatment. Recurrent strokes are extraordinarily rare in APMPPE (3,6,8), and all have occurred during corticosteroid taper (2,6,8).

CASE REPORT

A 43-year-old white man presented with bilateral visual loss. He had hypertension and long-standing hearing loss on the left, was obese, and was a cigarette smoker. Two weeks before his visual complaints, he had a fever of 101F. He subsequently developed a severe diffuse headache and was treated with antibiotics for presumed sinusitis. Soon thereafter he developed a central scotoma in his right eye, and 5 days later a similar scotoma in his left eye.

Results of brain MRI were normal. The headache persisted. Visual acuity was count fingers in his right eye and 20/200 in his left eye, and there were multiple placoid cream-colored lesions in both maculas (Fig. 1). Goldmann visual fields showed central scotomas in both eyes. A retinal fluorescein angiogram showed early blockage of the macular lesions and late staining suggestive of APMPPE (Fig. 2).

Results of an extensive infectious and inflammatory work-up were negative. Lumbar puncture showed 253 white cells/mm³ with 84% lymphocytes, normal glucose, and mildly elevated protein (57 mg/dL). Cytology

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and culture results were negative. These findings were considered consistent with lymphocytic meningitis. Intravenous methylprednisolone (250 mg every 6 hours) was administered for 3 days, followed by a taper of oral prednisone over 10 days.

Two weeks later he developed an acute left hemiparesis. Repeat MRI with diffusion images of the brain showed acute ischemia in the right middle cerebral artery distribution (Fig. 3). MRA suggested decreased flow within the distal right middle cerebral artery branches. A catheter cerebral angiogram demonstrated mild stenosis and dilation of branches of the right middle cerebral artery and anterior cerebral artery, suggesting small vessel vasculopathy (Fig. 4), presumably from vasculitis. Intravenous methylprednisolone (250 mg every 6 hours) was administered for 3 days, followed by a slow taper of oral prednisone to 10 mg/day. Treatment with cyclophosphamide (150 mg by mouth daily) was begun and continued for 6 months. The hemiparesis resolved over a few weeks. Six months later cyclophosphamide was discontinued and replaced by 50 mg azathioprine, and a maintenance dose of 10 mg/day prednisone.

Two weeks after discontinuation of cyclophosphamide, his headaches recurred, associated with confusion and dizziness. Brain MRI/MRA showed findings consistent with a new right middle cerebral artery (parietal) infarction. Repeat lumbar puncture showed 10 cells/mm³ with normal protein. He received 3 days of intravenous methylprednisolone (250 mg every 6 hours), and treatment with 150 mg cyclophosphamide daily was reinstated. His symptoms improved over a few days.

Three months later, his condition was stable with a regimen of 150 mg/day cyclophosphamide and 10 mg/day prednisone. The neurologic deficits continued to improve, with a lingering mild decrease in finger movement of the left hand. Visual acuity had improved to 20/80 in the right eye and 20/60 in the left eye with persistent alteration of the retinal pigment epithelium. Nine months later, he was still being treated with 150 mg/day cyclophosphamide and 5 mg/day prednisone. Results of the neuro-ophthalmologic examination were unchanged.

**DISCUSSION**

Our patient had two cerebral infarctions after his diagnosis of ophthalmic manifestations of APMPPE. The first infarction occurred within 2 weeks of the onset of the ophthalmic manifestations and shortly after corticosteroid
Recurrent Stroke with APMPPE

FIG. 3. FLAIR axial MRI shows multifocal hyperintensities in the right basal ganglia (A, arrow) and in the distal territory of the right middle cerebral artery (B, arrows), consistent with infarction.

treatment was tapered. The second infarction developed 6 months later, shortly after cyclophosphamide was replaced with azathioprine, suggesting that an exacerbation of central nervous system (CNS) vasculopathy may have been related to the change in medical therapy.

APMPPE rarely includes stroke. Table 1 presents a summary of the 18 well-documented reports of APMPPE associated with proven or presumed cerebral vasculitis or with cerebral venous thrombosis (2-13).

Although ophthalmic APMPPE affects men and women equally, our literature review suggests that neurologic complications are more frequent in men (Table 1) (2-13). Among the neurologic complications of APMPPE, headaches and cerebrospinal fluid (CSF) pleocytosis are most common (2,8,26). It is unclear, however, whether these features initiate more serious complications associated with cerebral vasculitis.

Cerebral complications, principally stroke, are most likely to occur simultaneously or within a few weeks of the ophthalmic diagnosis. In 3 patients, they have occurred simultaneously (3,13), and in 15 patients, within a few days to 6 years (median: 3 weeks) (2-12). In 1 patient, the ophthalmic manifestations occurred 3 months after the neurologic manifestations (3) (Table 1). Only 3 cases had a recurrent cerebral infarction (3,6,8), which developed 4 days after corticosteroids were discontinued in 1 patient (6) and during corticosteroid taper 1 week and 3 months after the first stroke (3,8).

CNS vasculopathy associated with APMPPE involves small and large arteries (lacunar and territorial infarctions). Only 10 of the reported patients had catheter cerebral angiography, with 9 showing small vessel vasculopathy. Lumbar puncture showed lymphocytosis in 9 of 12 patients (white blood cell count range 5-253 cells/mm³) and elevated protein in 7 of 13 patients (range 45-156 mg/dL), suggesting an inflammatory mechanism. However, the presumption of cerebral "vasculitis" as the pathologic process underlying neurologic involvement in APMPPE is mainly based on imaging findings (2-15). Multifocal segmental vessel narrowing observed on cerebral angiography is not specific to vasculitis and could also reflect vasospasm or other vasculopathies. There are only 2 case reports of patients with APMPPE that contain cerebral histopathologic descriptions (4,5). Only one report, an autopsy study, included both ocular and cerebral histopathologic findings (4). At the ocular level, granulomatous inflammation was seen beneath the RPE, not near the vessels, supporting inflammation but not the expected choroidal vasculitis. At the cerebral level, there was focal granulomatous vasculitis affecting large cerebral arteries in agreement with the only other documented histopathologic

FIG. 4. Catheter cerebral angiography (A, lateral view; B, frontal view) shows irregularity and mild stenosis of the branches of the right middle cerebral and anterior cerebral arteries (arrows), consistent with vasculopathy.
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<tr>
<th>Reports (ref)</th>
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<th>Neurologic Symptoms and Signs</th>
<th>Delay Between Ocular and CNS Manifestations</th>
<th>Imaging Findings</th>
<th>Cerebrospinal Fluid Findings</th>
<th>Treatment</th>
<th>Histopathology Findings</th>
<th>Outcome</th>
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<td>Holt et al., 1976 (2)</td>
<td>22/M</td>
<td>Photophobia; bilateral APMPPE</td>
<td>Headache, aphaisia, weakness</td>
<td>3 days after visual complaints</td>
<td>CNS involvement</td>
<td>WC: 177 cells (\text{mm}^3) (lymphocytes)</td>
<td>100 mg/day prednisone for 10 days, then taper</td>
<td>No</td>
<td>Asymptomatic at 36 months</td>
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<tr>
<td>Sigelman et al., 1979 (7)</td>
<td>18/M</td>
<td>Bilateral visual loss; APMPPE</td>
<td>Headache, homonymous hemianopia</td>
<td>4 days after visual complaints</td>
<td>CNS involvement</td>
<td>WC: 5 cells (\text{mm}^3) (lymphocytes)</td>
<td>No treatment</td>
<td>No</td>
<td>Persistent homonymous hemianopia</td>
</tr>
<tr>
<td>Smith et al., 1983 (6)</td>
<td>25/M</td>
<td>Photophobia; bilateral APMPPE</td>
<td>Headache, homonymous hemianopia</td>
<td>2 months after visual complaints (3 days after prednisone discontinued)</td>
<td>CNS involvement</td>
<td>“Lymphocytosis”; “Elevated protein level”</td>
<td>60 mg/day prednisone</td>
<td>No</td>
<td>1 exacerbation between treatment courses</td>
</tr>
<tr>
<td>Weinstein et al., 1988 (11)</td>
<td>23/M</td>
<td>Bilateral visual loss; APMPPE</td>
<td>Numbness, blurred speech, followed 1 month later by homonymous hemianopia</td>
<td>2-3 months after diagnosis of APMPPE</td>
<td>CNS involvement</td>
<td>WC: 9 cells (\text{mm}^3) (96% lymphocytes)</td>
<td>1 g/day methylprednisolone IV for 3 days then oral taper over 4 months</td>
<td>No</td>
<td>Persistent homonymous hemianopia</td>
</tr>
<tr>
<td>Wilson et al., 1988 (5)</td>
<td>24/M</td>
<td>Bilateral visual loss; APMPPE</td>
<td>Headache, seizure</td>
<td>2 weeks after diagnosis of APMPPE (while receiving prednisone)</td>
<td>No information</td>
<td>WC: 0</td>
<td>Protein: 66 mg/dL</td>
<td>Leptomeningeal biopsy; granulomatous cerebral arteritis</td>
<td>Died after 2 days of 40 mg/day prednisone for 2 weeks, then taper to 20 mg/day</td>
</tr>
<tr>
<td>Hammer et al., 1989 (6)</td>
<td>25/W</td>
<td>Bilateral visual loss; APMPPE</td>
<td>Hemiparesis</td>
<td>3 weeks after diagnosis of APMPPE (while receiving 20 mg/day prednisone)</td>
<td>CT: cerebral infarctions in anterior and middle cerebral artery territories</td>
<td>No LP</td>
<td>40 mg/day prednisone</td>
<td>No</td>
<td>Died (cerebral herniation) within 48 hours while receiving 40 mg/day prednisone</td>
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<tr>
<td>Reports (ref)</td>
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<td>Ocular Symptoms and Signs</td>
<td>Neurologic Symptoms and Signs</td>
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<td>Stoll et al, 1991 (12)</td>
<td>54, M</td>
<td>Bilateral visual loss 12 hours between each eye: APMPPE</td>
<td>Dysarthria, weakness, ataxia</td>
<td>CNS involvement 4 months after diagnosis of APMPPE</td>
<td>MRE: multiple hemispheric white matter lesions Cerebral angiogram: small vessel vasculopathy</td>
<td>WC: 18 cells mm(^3) (lymphocytes) Protein: 67 mg/dL.</td>
<td>24 mg dexmethasone IV for 6 days, followed by oral taper over 2 months 150 mg/day azathioprine</td>
<td>No</td>
<td>Asymptomatic at 1 year</td>
</tr>
<tr>
<td>Bewerneyer et al, 1993 (10)</td>
<td>27, M</td>
<td>Photophobia followed 1 week later by bilateral visual loss: APMPPE</td>
<td>Hemiparesis, stupor, slurred speech, nystagmus</td>
<td>CNS involvement 5 months after diagnosis of APMPPE</td>
<td>MRE: right pontine infarction</td>
<td>WC: 55 cells mm(^3) (Lymphocytes) Protein: 36 mg/dL.</td>
<td>100 mg/day prednisone tapered over 6 weeks 150 mg/day azathioprine</td>
<td>Muscle biopsy (tibialis anterior muscle): vasculitis</td>
<td>Asymptomatic at 2 years</td>
</tr>
<tr>
<td>Comu et al, 1996 (8)</td>
<td>23, W</td>
<td>Bilateral visual loss: APMPPE</td>
<td>Headache, hemiparesis</td>
<td>CNS involvement 3 weeks after diagnosis of APMPPE (while receiving steroids)</td>
<td>MRE: bilateral parieto-occipital infarctions Cerebral angiogram: normal</td>
<td>“Lymphocytosis” Protein: 45 mg/dL.</td>
<td>1 g/day methylprednisolone IV, then taper cyclophosphamide added when relapse (total duration of treatment: 12 months)</td>
<td>No</td>
<td>Right parietal infarction when steroid tapered to 40 mg/day; no relapse at 24 months with cyclophosphamide</td>
</tr>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>16, M</td>
<td>Scotomas in the left eye: bilateral APMPPE</td>
<td>Seizure, followed 1 month later by HA and numbness</td>
<td>CNS involvement 1 year after diagnosis of APMPPE</td>
<td>MRE: biventricular hemiinjuries Cerebral angiogram: superior sagittal sinus thrombosis</td>
<td>WC: 28 cells mm(^3) (lymphocytes) Protein: 85 mg/dL.</td>
<td>100 mg/day prednisone taper</td>
<td>Brain biopsy: normal</td>
<td>No relapse at 13 months</td>
</tr>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>25, M</td>
<td>Posterior uveitis, visual loss in the right eye: bilateral APMPPE</td>
<td>Headache, hemiparesis 1 month after diagnosis of uveitis, during prednisone taper</td>
<td>Diagnosis of APMPPE 3 months after CNS involvement</td>
<td>MRE: normal Cerebral angiogram: small vessel vasculopathy</td>
<td>No LP</td>
<td>“Systemic steroids”: 50-200 mg/day cyclophosphamide (total duration of treatment &lt;6 months)</td>
<td>No</td>
<td>No relapse at 5 years</td>
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<tbody>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>36/M</td>
<td>Bilateral visual loss: APMPPE</td>
<td>Numbness</td>
<td>CNS involvement 3 weeks after diagnosis of APMPPE (during steroid taper)</td>
<td>MRI: multiple T2 abnormalities in thalamus and periventricular white matter</td>
<td>Protein: 88 mg/dL</td>
<td>Methylprednisolone IV for 5 days with oral taper</td>
<td>No</td>
<td>Persistent numbness at 2 months</td>
</tr>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>44/W</td>
<td>APMPPE 6 years previously</td>
<td>Numbness</td>
<td>CNS involvement 6 years after diagnosis of APMPPE</td>
<td>MRI: small enhancing lesion at left midbrain-pontine junction and 2 smaller periventricular white matter T2 lesions</td>
<td>N/A</td>
<td>Methylprednisolone IV with oral taper; repeat courses of IV methylprednisolone for progression of MRI changes</td>
<td>No</td>
<td>Progression of MRI lesions over following 3 years</td>
</tr>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>39/W</td>
<td>Bilateral APMPPE diagnosed 4 months after episodes of transient visual loss in right eye</td>
<td>Headache</td>
<td>Simultaneous (by imaging)</td>
<td>MRI: right parietal contrast-enhancing lesion</td>
<td>Normal</td>
<td>Methylprednisolone IV then oral taper</td>
<td>No</td>
<td>Asymptomatic at 2 months</td>
</tr>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>27/W</td>
<td>Visual loss right eye; bilateral APMPPE; 2 years later; visual loss left eye</td>
<td>None</td>
<td>CNS involvement (by imaging) 2 years after diagnosis of APMPPE</td>
<td>MRI: multiple periventricular T2 lesions</td>
<td>Normal</td>
<td>Dose pack methylprednisolone</td>
<td>No</td>
<td>At 3 months vision had returned to normal</td>
</tr>
<tr>
<td>O’Halloran et al, 2001 (3)</td>
<td>51/M</td>
<td>Bilateral APMPPE</td>
<td>Homonymous hemianopia</td>
<td>Simultaneous</td>
<td>MRI: infarction in right temporal lobe</td>
<td>No LP</td>
<td>Intravenous steroids followed by oral taper</td>
<td>No</td>
<td>Persistent homonymous hemianopia; no relapse at 18 months</td>
</tr>
<tr>
<td>de Vries, 2006 (4)</td>
<td>23/M</td>
<td>Visual loss right eye: bilateral APMPPE</td>
<td>Headache, hemiparesis, numbness, seizure</td>
<td>CNS involvement 3 days after diagnosis of APMPPE</td>
<td>MRI MRA: occlusion of left middle cerebral artery and narrowing of the right posterior cerebral artery with infarction</td>
<td>No LP</td>
<td>No treatment</td>
<td>Autopsy: granulomatous inflammation of the choroid and brainstem</td>
<td>Died from cerebral herniation</td>
</tr>
<tr>
<td>Reports (ref)</td>
<td>Age/ Sex</td>
<td>Ocular Symptoms and Signs</td>
<td>Neurologic Symptoms and Signs</td>
<td>Delay Between Ocular and CNS Manifestations</td>
<td>Imaging Findings</td>
<td>Cerebrospinal Fluid Findings</td>
<td>Treatment</td>
<td>Histopathology Findings</td>
<td>Outcome</td>
</tr>
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</tr>
<tr>
<td>Klise et al., 2007 (13)</td>
<td>29 M</td>
<td>Bilateral visual loss: APMPPE</td>
<td>Headache, sinus congestion</td>
<td>Simultaneous (imaging findings at time of APMPPE diagnosis)</td>
<td>CT/ CTA: pansinusitis, bilateral cavernous sinus thrombosis</td>
<td>No LP</td>
<td>Surgical drainage of sinuses, antibiotics and anticoagulation</td>
<td>No</td>
<td>At 16 months, persistent partial left third nerve palsy</td>
</tr>
<tr>
<td>Present case</td>
<td>43 M</td>
<td>Bilateral visual loss: APMPPE</td>
<td>Headache, hemiparesis</td>
<td>CNS involvement 2 weeks after diagnosis of APMPPE (during steroid taper)</td>
<td>MRI/MRA: infarction in the right middle cerebral artery</td>
<td>WC: 253 cells/mm³ (84% lymphocytes)</td>
<td>1 g/day methylprednisolone IV for 3 days followed by oral taper: 150 mg/day cyclophosphamide, then azathioprine after 6 months</td>
<td>No</td>
<td>6 months later, new infarction while changing cyclophosphamide to azathioprine and still receiving 10 mg day prednisone</td>
</tr>
</tbody>
</table>

*Autopsy findings: granulomatous choroidal inflammation with Langhans multinucleated giant cells and focal disruption of the retinal pigment epithelium; granulomatous cerebral arteritis with Langhans-type cells at the level of the lamina elastica interna. APMPPE, acute posterior multifocal placoid pigment epitheliopathy; CNS, central nervous system; CT, computed tomography; CTA, CT angiography; IV, intravenous; LP, lumbar puncture; M, man; W, woman; WC, white blood cell count.
study of cerebral vasculitis in association with APMPPE (5). One patient had vasculitis demonstrated on muscle biopsy (10). All other patients, including ours, are presumed to have had vasculitis without pathologic confirmation (27).

Three of the reported patients with APMPPE had fatal cerebral infarctions (4,5,9), which occurred 3 days (4), 2 weeks (5), and 3 weeks (9) after visual loss. Most other reported strokes in patients with APMPPE produced only minor residual neurologic deficits (2,3,6,10,12). Patients with APMPPE and neurologic manifestations have generally been treated with corticosteroids (16 of 19 patients), either orally (9 patients) or intravenously (7 patients). Five patients also received immunosuppressive azathioprine or cyclophosphamide (3,8,10,12). The two reported patients with APMPPE associated with cerebral venous thrombosis (3,13) had a good neurologic outcome.

The small number of reported cases does not allow definite recommendations regarding the management of patients with APMPPE limited to the eyes. However, because neurologic manifestations (usually stroke) are so rare in APMPPE, it is reasonable to limit brain imaging to patients developing unusual headaches or other neurologic symptoms. Imaging should include a brain MRI with diffusion images. Treatment should be based on the severity of clinical presentation, ranging from corticosteroids alone for headaches to other immunosuppressive agents for patients with imaging evidence of cerebral vasculopathy. Although only very few cases provide pathologic support for the theory that the underlying mechanism is inflammatory, it is reasonable to prescribe high-dose intravenous corticosteroids and other immunosuppressive therapy in patients with associated cerebral vasculopathy, as recommended for patients with primary CNS vasculitis (8).

REFERENCES

Dynamic MRA With Four-Dimensional Time-Resolved Angiography Using Keyhole at 3 Tesla in Head and Neck Vascular Lesions

Hemant Parmar, MD, Marko K. Ivancevic, PhD, Nancy Dudek, BS, Dheeraj Gandhi, MD, and Suresh K. Mukherji, MD

Abstract: Conventional MRA provides inadequate visualization of the dynamic features of blood flow in vascular lesions of the head and neck. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) is a new technique of performing contrast-enhanced MRA. By combining parallel imaging with sensitivity encoding (SENSE) with the keyhole imaging technique and a high field strength (3 T) magnet, we have been able to obtain detailed hemodynamic information similar to that obtained via catheter angiography with digital subtraction (DSA), but without the risks associated with ionizing radiation exposure, iodizing contrast agents, or catheterization itself.


Catheter angiography with digital subtraction (DSA) is the standard technique for imaging of the craniocervical vessels. With this technique, it is possible to obtain very high temporal resolution with three-dimensional (3D) reformats of multiple rotational datasets. However, because of the risks of arterial catheterization, the risks of ionizing radiation, and the costs of such procedures, safer angiographic procedures are being developed.

MRA has gained wide clinical acceptance in evaluation of the arterial and venous anatomy of the head, neck, and spine. The two- and three-dimensional flow-sensitive MRA sequences used traditionally, such as time-of-flight (TOF) (1,2), are limited by flow-related artifacts, low spatial resolution (compared with DSA), and lack of temporal resolution (3). They are gradually being supplanted by gadolinium contrast-enhanced magnetic resonance angiography (CE-MRA), particularly in visualization of high flow intracranial arteriovenous malformations (AVMs) and arteriovenous fistulas (AVFs).

CE-MRA produces high-resolution 3D volume acquisitions, but the exact timing is critical for obtaining optimal image quality and accurate vasculature depiction. Centric elliptic k-space ordering has been traditionally used to acquire the peak of arterial contrast and to avoid edge enhancement artifacts (1). Contrast-enhanced timing-robust angiography (CENTRA) was subsequently introduced, wherein the first 4 seconds part of the central k-space is sampled randomly to sample a larger window of the arterial phase (4). Routine 3D contrast-enhanced sequences reduce some of the flow-related artifacts of TOF MRA but do not provide temporal resolution in complex lesions (5). The scan duration of a complete MRA acquisition is too long to run dynamic MRA. Limitations of a single time point acquisition include lack of dynamic information and occasionally a mistimed bolus with resultant suboptimal vessel signal or venous contamination. To image dynamic contrast kinetics, techniques based on undersampling of k-space profiles, such as temporal interpolation of k-space views (6) and keyhole (7), were initially proposed.

Recently, four-dimensional time-resolved angiography using keyhole (4D-TRAK) has been introduced by combining CENTRA with parallel imaging with sensitivity encoding (SENSE) (8,9), half scan, and the keyhole technique (Fig. 1). With 4D-TRAK it became possible to accelerate dynamic MRA scans up to 60 times to a subsecond temporal sampling rate and follow contrast hemodynamics with the near-isotropic spatial resolution of 1–1.5 mm. Furthermore, a 3-T field strength magnet provides a higher signal/noise ratio that can be used to obtain images with higher spatial resolution. These
improvements have allowed dynamic 3D MRA to reach a performance closer to that of DSA than achieved with other MRA techniques. We review our experience with 4D-TRAK at 3 T in evaluation of vascular abnormalities in the head and neck.

METHODS

Contrast-enhanced dynamic MRA with 4D-TRAK was performed on a 16-channel 3.0-T Achieva system (Philips Medical Systems, Best, The Netherlands) equipped with a commercially available eight-channel SENSE-capable head coil. Patients were positioned with a 20-gauge intravenous catheter inserted into the antecubital vein. An automated power injector (Spectris Solaris; Medrad, Warrendale, PA) was used in a biphasic injection protocol. Gadobenate dimeglumine (Multihance, 20 mL; Bracco Diagnostics Inc., Milan, Italy) was injected initially at a flow rate of 2 mL/s followed by a saline flush of 25 mL at a flow rate of 2 mL/s. The 4D MRA sequence was started immediately after the contrast injection (injection and scanning simultaneously).

4D-TRAK images were acquired using the keyhole method (7,10), partial Fourier, and CENTRA (11). In CENTRA, a central k-space cylinder is randomly filled, allowing for k-space sampling during the whole passage of the contrast bolus over time. The periphery of k-space was collected in the reference dataset at the end of the acquisition in an elliptical order, and the resulting data were used for reconstruction of each of the dynamic phases as described in the keyhole approach (Fig. 1).

In addition to the CENTRA keyhole method, SENSE was implemented. The SENSE technique was used with a reduction factor of 3–3.2 in the phase-encoding direction and a reduction factor of 1.8 in the slice-encoding direction, yielding a total acceleration factor (AF) of 3.18. Furthermore, partial Fourier imaging was added, skipping 25% of k-space, and accelerating the k-space sampling by a factor of 1.33. Combining the techniques of 4D-TRAK yielded a total acceleration of approximately 33.75. That is, if a conventional 3D MRA required 33.75 seconds at the specified spatial resolution, it can be acquired dynamically every 1 second by this technique. Each of the individual
FIG. 3. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) magnetic resonance venography (MRV) in a normal study. A. Sagittal maximal intensity projection (MIP) of acquired image series. B. Sagittal MIP after subtraction of early arterial phase preferentially displays venous kinetics.

FIG. 4. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of an intracranial arteriovenous malformation (AVM). Coronal (A) and sagittal (B) maximal intensity projection images show a large AVM nidus in the left frontal lobe (arrowheads) with feeders from multiple frontal branches of the left anterior and middle cerebral arteries. Venous drainage is through a severely dilated left frontoparietal vein draining into the superior sagittal sinus and a large draining vein (arrows) emptying into the superior sagittal sinus. Deep drainage into the internal cerebral veins and vein of Galen is especially well seen on the sagittal images (arrows).
acceleration parameters can be adjusted to achieve up to AF = 60 on our system.

Image processing included mask subtraction to suppress the background signal of the stationary tissue. For this purpose, we used one of three dynamic volumes acquired before administration of the contrast agent with the same time-resolved MRA sequence. Depending on the field of view, resolution, and coverage adjustments on individual patients, the temporal resolution range was 1.6–3 seconds in the brain and 1.9–4.8 seconds in the carotid arteries. The in-plane acquired resolution range was 0.6–1 mm.

RESULTS

Dynamic MRA and magnetic resonance venography (MRV) of the head and neck using 4D-TRAK allowed the visualization of arterial, intermediate, and venous phases of vessel enhancement (Figs. 2 and 3). Anatomical detail and temporal information were obtained. Representative examples are illustrated in Figures 2 through 11.

Intracranial AVMs and AVFs

With dynamic MRA with 4D-TRAK at 3 T, it was possible to correctly identify the normal vasculature, enlarged arterial pedicles, lesion nidus, and venous drainage pattern of an AVM and to resolve arterial and venous structures separately (Fig 4). In an AVF (Fig. 5), medium- and large-sized arterial pedicles were readily visualized, and synchronous opacification of the diseased sinus or vein indicated the arteriovenous shunt. Sometimes in AVF the direct arterial feeders or the fistula was too small.

FIG. 5. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of an intracranial arteriovenous fistula (AVF). Coronal maximal intensity projection images of dynamic MRA show a large tangle of vessels in the region of the left superior orbital fissure. The arterial feeders include branches from the left internal maxillary artery, left superficial temporal artery, and left ophthalmic artery (arrows). There are large venous varices within the left cavernous sinus, and some drainage is via the left superficial middle cerebral veins (arrowheads). There was no discrete nidus seen, suggesting that this is a fistula rather than a vascular malformation.
to visualize, but visualization of early filling of the corresponding vein or dural sinus would point to this abnormality. A more focused and thorough evaluation of these vessels could then be performed with DSA.

Dural Venous Sinus Thrombosis
Although 4D-TRAK provided imaging similar to that of single-phase contrast-enhanced MRV, we found that it yielded added information about venous flow patterns, collateral circulation, and intracranial circulation times, which allowed for better evaluation of this condition (Fig. 6) (12).

Orbital and Neck Vascular Malformations
As with intracranial AVMs, dynamic MRA with 4D-TRAK was helpful in correctly identifying normal vasculature, enlarged arterial pedicles (Fig. 7), the lesion nidus, and the venous drainage pattern in orbital AVMs (Fig. 8). MRI had the added advantage of visualization of the surrounding soft tissues. We also found this technique useful in post-treatment studies of head and neck AVMs (Fig. 7C).

Carotid Body Tumor
In highly vascular tumors such as carotid body tumors (paragangliomas), visualization of early arterial phase-contrast...
FIG. 7. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of an orbital arteriovenous malformation (AVM). Sagittal (A) and coronal (B) maximal intensity projection images show a large AVM (arrowheads) in the right orbital region fed by the branches of the right external carotid artery and left ophthalmic artery (arrows). A large draining vein extends over the supraorbital ridge and empties into the angular facial vein (large arrows). A three-dimensional time of flight magnetic resonance angiogram (C) shows the enlarged arterial feeders from the external carotid artery and the ophthalmic artery (arrows), but it does not provide details of the venous drainage.
FIG. 8. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of an orbital venolymphatic malformation. 
A. Postcontrast T1 coronal MRI shows a mass (arrowheads) with a small intracranial component (arrows). B. Sagittal MIP images show it as a large vascular malformation (arrowheads) with a small apical varix (arrows).

enhancement within the tumor was helpful in making a correct diagnosis, as other tumors of the carotid space (such as lymphoma and nerve sheath tumor) do not show this early enhancement (Fig. 9). Such information is also helpful in guiding the surgeon during preoperative embolization.

Carotid Artery Stenosis/Fibromuscular Dysplasia

Using an extended field of view, the arch of the aorta and cervical and cerebral vessels could be demonstrated simultaneously in a single image. In patients with advanced atherosclerosis (Fig. 10) or fibromuscular dysplasia (Fig. 11), delayed filling of the cerebral vessels was sometimes observed on the side of the stenotic or occluded carotid vessel (13,14). It was possible to demonstrate the patency of the distal vasculature and assess the compensatory collateral circulation. Although the information obtained from this study is analogous to that obtained by catheter angiography, the degree of stenosis was difficult to estimate accurately, and

FIG. 9. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of a carotid body tumor. A. Postcontrast T1 axial fat-suppressed MRI shows an avidly enhancing mass in the right carotid space (arrowheads) that displaces vessels (arrows). B. Coronal maximal intensity projection images show early and rapid contrast enhancement of the mass, suggestive of a carotid body tumor, a diagnosis confirmed at surgery.
FIG. 10. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of a carotid artery stenosis. Coronal maximal intensity projection images show severe stenosis of the proximal segments of both internal carotid arteries (arrows).

other techniques such as single phase-contrast enhanced MRA or CT angiography had to be coupled with dynamic MRA.

DISCUSSION

We have shown cases in which 4D-TRAK imaging provided more complete hemodynamic information of the arterial and venous system in head and neck lesions than could be seen with conventional MRA. Arterial and venous phases could be separated either by simple subtraction, as used here (Fig. 3), or by more sophisticated post-processing methods based on correlation (15) or contrast arrival time (CAT) maps (16).

Because 4D-TRAK forces a loss of high spatial resolution to achieve high temporal resolution, 3-T field strength is essential. To identify the more subtle features such as flow-related aneurysms or intranidal fistulas, dynamic MRA must be performed in combination with single-phase MRA, as suggested by Nael et al (17), or one must use catheter angiography.

Dynamic MRA with 4D-TRAK covers the full 3D volume with adequate spatial and temporal resolution without the risks of ionizing radiation exposure, iodizing contrast agents, or catheterization itself. The 4D-TRAK technique can be applied to arterial bypass procedures to image the shunt without the risk of arterial damage from direct catheterization and to subclavian steal syndrome to demonstrate the delayed opacification of the vertebral artery (13).

Although promising, this technique is not without its limitations. It requires a dedicated team consisting of a neuroradiologist, magnetic resonance physicist, and magnetic resonance technologist to adjust scanning parameters. The most significant drawback of this approach is that one must prospectively decide to favor either spatial or temporal features at the expense of the other. The current technique has relatively low spatial resolution, a problem especially in the evaluation of small AVFs, in which small fistulous portions may not be readily apparent. Improved software and higher field strength magnets will probably mitigate this problem in the future.
Dynamic MRA

FIG. 11. Four-dimensional time-resolved angiography using keyhole (4D-TRAK) of fibromuscular dysplasia. Coronal maximal intensity projection images show multiple areas of vascular narrowing and dilatation, giving rise to a “beaded” appearance (arrows) of the internal carotid and vertebral arteries.

REFERENCES


Bilateral Optic Neuritis in Acute Hepatitis C

Junaid Siddiqui, MD, Jacinthe Rouleau, MD, Andrew G. Lee, MD
Yutaka Sato, MD, and Michael D. Voigt, MD

Abstract: A 34-year-old woman developed bilateral optic neuritis 2 weeks after the onset of acute hepatitis C. The strong temporal relationship between the initial clinical manifestations of hepatitis C and the development of optic neuritis provides a basis for thinking that the hepatitis caused the optic neuritis. After corticosteroid treatment, the optic neuropathy markedly improved but left behind retinal nerve fiber thinning, as measured by optical coherence tomography, and optic disc pallor. Optic neuritis has been reported in conjunction with hepatitis A and B but not with hepatitis C.


Postinfectious optic neuritis occurs in association with a number of bacterial and viral infections, including those due to adenovirus, Coxsackie virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, measles, mumps, rubella, rubella, varicella and herpes zoster, and rarely hepatitis A (1,2) and B (3-5).

Optic neuritis has not been reported in association with acute hepatitis C, a major global health problem that affects an estimated 170 million people worldwide. It causes chronic hepatitis, which may lead to cirrhosis in up to 20% of chronically infected individuals, and is now the leading indication for liver transplantation (6). Frequently asymptomatic, it can also present with acute severe hepatitis and extrahepatic complications (7,8). We report a case of bilateral optic neuritis in a patient with acute hepatitis C.

CASE REPORT
A 34-year-old woman presented with jaundice, dark urine, myalgia, nausea, vomiting, and dysuria. Serum transaminase levels were markedly elevated in keeping with acute hepatitis (Fig. 1).

She had not used any hepatotoxic medications or acetaminophen. Hepatitis C virus (HCV) antibodies were positive, and HCV RNA was present at a level of 300 IU/ml with genotype 1a. Results for hepatitis B surface antigen, hepatitis B core IgM antibodies, autoimmune hepatitis markers (anti-nuclear, anti-mitochondrial, anti-smooth muscle, and anti-atypical P- neutrophil cytoplasmic antibodies), cytomegalovirus DNA, and acute antibodies to Epstein-Barr virus were all negative. Liver ultrasound showed a normal-sized liver and spleen. Liver biopsy (Fig. 2) showed a heavy infiltrate of lymphocytes in the portal and lobular areas in keeping with acute hepatitis. Klatsskin stain showed normal architecture and minimal fibrosis. A diagnosis of acute hepatitis C was established.

Fourteen days after the onset of these symptoms, she developed a headache, her eyes became red and she reported worsening vision in both eyes. Visual acuity was 20/200 in the right eye and 20/50 in the left eye with pinhole at a bedside examination. Pupils measured 4 mm in the dark and 3 mm in the light with a 0.3-log unit relative afferent pupil defect in the right eye. Ocular motility and alignment were normal. The anterior ocular segment appeared normal. There was mild optic disc edema in both eyes. Goldmann perimetry showed dense cecocentral scotomas in both eyes (Fig. 3A). Results of neurologic examination were otherwise normal.

Retinal fluorescein angiography showed bilateral optic disc hyperfluorescence consistent with optic disc edema. Optical coherence tomography (OCT) of the peripapillary retina using the fast retinal nerve fiber layer thickness protocol showed an average thickness of 138 um in the right eye and 107 um in the left eye (normal 100 ± 11 um). Brain MRI showed T2 high signal, enlargement, and enhancement of the intraorbital and intracranial segments of both optic nerves and enhancement of the optic chiasm without other abnormalities (Fig. 4).

Results of chest x-ray, complete blood count (CBC), erythrocyte sedimentation rate (ESR), and serum protein electrophoresis; serum rapid plasma reagin (RPR), Lyme disease titer, toxoplasma, and Bartonella henselae antibodies; viral studies for cytomegalovirus, Epstein-Barr
virus, enterovirus and herpes simplex, and serum doublestranded DNA, cryoglobulins, and rheumatoid factor were normal or negative. Serum angiotensin-converting enzyme (ACE) was marginally elevated at 58 U/L (normal 3-52 U/L), but she had no other clinical or chest X-ray findings compatible with sarcoidosis. Cerebrospinal fluid (CSF) analysis was normal, including VDRL and fluorescent treponemal antibodies. Paired serum and CSF immunofixation electrophoresis revealed a CSF IgG of 8% (normal 0-14%), a CSF IgG index of 0.5 (normal 0.0-0.7), and de novo synthesis of 1.7 mg/day (normal 9.9 to 3.3 mg/day).

She was treated with 1 g intravenous methylprednisolone daily for 3 days followed by a 14-day oral taper. Six weeks after the corticosteroid treatment was started and before the start of HCV treatment, visual acuity had

FIG. 1. Time course of biochemical changes of the acute hepatitis C. Day 0 was the day of the first medical encounter. Visual symptoms antedated day 0 by 3 weeks.

FIG. 2. Liver biopsy demonstrates dense portal lymphocytic infiltrate (black arrows), interface hepatitis (white arrow), preserved architecture (right inset), and liposome-laden sinusoidal macrophages (black arrowheads, left inset). (Hematoxylin and eosin, X400; right inset Klatskin stain, X100; left inset periodic acid Schiff stain, X400.)
FIG. 3. A. Goldmann perimetry at presentation shows dense cecocentral scotomas with breakout inferiorly in both eyes. B. Goldmann perimetry performed 14 weeks later shows improvement after treatment with corticosteroids.

improved to 20/40 in the right eye and 20/30 in the left eye. Pegylated interferon and ribavirin therapy for hepatitis C was started 72 days after the onset of her initial symptoms of acute hepatitis and approximately 8 weeks after the initial ophthalmologic examination (Fig. 1).

Follow-up examination at 4 months after presentation showed that her vision had markedly improved to 20/20 in both eyes, but both optic discs were pale (Fig. 5). Goldmann visual fields were improved (Fig. 3B). Repeat OCT confirmed thinning of the retinal nerve fiber layer measurements of 64 um in the right eye and 60 um in the left eye. Seven months after the initial presentation, her acute hepatitis had resolved. She had no detectable serum HCV RNA after completion of pegylated interferon and ribavirin therapy,

**DISCUSSION**

The striking feature of this case is the clear temporal relationship between the onset of acute hepatitis C and optic neuritis, making a strong case for hepatitis C as the cause. There have been prior reports of optic neuritis associated with acute hepatitis A and B, but not hepatitis C (Table 1). Jouhadi et al(1) described a case of neuromyelitis

FIG. 4. Brain MRI at presentation. Precontrast (A) and postcontrast (B) coronal T1 studies show enhancement of both intraorbital optic nerves (arrows). Coronal T2 study (C) shows an abnormally high signal in both intraorbital optic nerves (arrows).
TABLE 1. *Publications of viral hepatitis-associated optic neuritis*

<table>
<thead>
<tr>
<th>Publications</th>
<th>Age</th>
<th>Sex</th>
<th>Hepatitis Type</th>
<th>Time to Onset (days)*</th>
<th>Uni/Bil</th>
<th>Optic Nerve/Tract Imaging</th>
<th>Corticosteroid Treatment</th>
<th>Outcome</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jouhadi et al (1)</td>
<td>8</td>
<td>F</td>
<td>A</td>
<td>27</td>
<td>Bil</td>
<td>T2 hyperintensity of optic nerve</td>
<td>1 g 1.75 m2 methylprednisone, BSA IV and 2 g/kg IV 1g day 1; 2 mg/kg day prednisone</td>
<td>3 months</td>
<td>“Total recovery” “Total recovery”</td>
</tr>
<tr>
<td>McKibbin et al (2)</td>
<td>22</td>
<td>F</td>
<td>A</td>
<td>28</td>
<td>Bil</td>
<td>Brain and optic nerve CT and MRI “normal”</td>
<td>IV methylprednisone and oral prednisone</td>
<td>6 month</td>
<td>OD 6/12, OS 6/5</td>
</tr>
<tr>
<td>Achiron (3)</td>
<td>41</td>
<td>F</td>
<td>B</td>
<td>31</td>
<td>Bil</td>
<td>Not specified (brain MRI “normal”)</td>
<td>100 mg day prednisone</td>
<td>6 wks</td>
<td>OD 6/6, OS 6/6</td>
</tr>
<tr>
<td>Albitar et al (9)</td>
<td>28</td>
<td>M</td>
<td>B</td>
<td>7</td>
<td>Bil</td>
<td>Cerebral scan: unusual CT; “edema” of optic nerve</td>
<td>60 mg/day prednisone; 60 mg/day prednisone</td>
<td>40 days</td>
<td>10/10 OU</td>
</tr>
<tr>
<td>Galli et al (5)</td>
<td>33</td>
<td>M</td>
<td>B</td>
<td>40</td>
<td>Uni</td>
<td>CT: “edema” of optic nerve</td>
<td>60 mg/day prednisone</td>
<td>40 days</td>
<td>10/10 OU</td>
</tr>
<tr>
<td>Siddiqui et al (current report)</td>
<td>34</td>
<td>F</td>
<td>C</td>
<td>14</td>
<td>Bil</td>
<td>T2 hyperintensity of optic nerve and tracts, T1 enhancement of optic nerve</td>
<td>1 g IV methylprednisone for 3 days; prednisone 60 mg day</td>
<td>14 days</td>
<td>20/20 OU</td>
</tr>
</tbody>
</table>

Bil, bilateral; BSA, body surface area; Gad, gadolinium MRI contrast; IV, intravenous; IVlg, intravenous immunoglobulin; OD, left eye; OS, right eye; OU, both eyes; Uni, unilateral.

*Time from onset of first symptoms of hepatitis to onset of first visual symptoms.

*Protocol of taper not specified.

Acuity represents best corrected visual acuity.

§Color represents color vision to Ishihara plates.

¶Dose not given.

¶Not further described.
with bilateral simultaneous papillitis in an 8-year-old child after acute viral hepatitis A infection. An additional case of bilateral optic neuritis after hepatitis A with good visual recovery was reported (2). Achiron (3) presented a case of bilateral optic neuritis associated with systemic vasculitis and glomerulonephritis after acute hepatitis B. Galli et al (5) described a unilateral retrobulbar optic neuritis in a 33-year-old woman with acute hepatitis B. Albitar et al (9) reported a case of retrobulbar optic neuritis after recombinant hepatitis B vaccination in a patient with end-stage renal disease.

In prior cases of viral hepatitis-associated optic neuritis, four of five cases were bilateral with optic disc edema at onset, whereas one case of hepatitis B was associated with unilateral retrobulbar optic neuritis.

The time from the onset of the systemic viral symptoms to the ophthalmic symptoms in our patient was similar to that of previously reported patients (7—40 days) and she seemed to have a similar favorable response to high-dose corticosteroid treatment. However, although visual symptoms improved or resolved in all cases after corticosteroid treatment, all patients, with the exception of the patient of Jouhadi et al (1), were left with impairment of visual acuity, color vision, or visual field or pallor of the optic discs. MRI abnormalities in our patient were similar to those reported by McKibbin in hepatitis A (2). However, MRI was reported to be normal in three other reports (Table 1) (1,3,9), two of which appeared in the mid-1990s when imaging technology was less sensitive.

The mechanism for optic neuritis in patients with acute hepatitis is unknown. Complement activation and autoimmune-mediated neurotoxicity have been proposed. Galli et al (5) described a unilateral retrobulbar optic neuritis in a 33-year-old woman with acute hepatitis B and found that complement activation, involving both classic and alternative pathways, and high levels of circulating immune complexes were present at the onset of ophthalmic symptoms.

HCV is associated with autoimmune or lymphoproliferative states perhaps related to the propensity of the virus to replicate in lymphoid cells (10). Mixed cryoglobulinemia associated with hepatitis C can result in vasculitis, causing weakness, arthralgia, purpura, glomerulonephritis, and mononeuritis multiplex (11,12). Cryoglobulinemia may cause cerebral vasculitis (13-19) or leukoencephalopathy (20). However, there was no evidence clinically, by fluorescein angiography, or by brain imaging of vasculitis in our patient, and she did not have cryoglobulinemia. There is evidence that central nervous system (CNS) replication of HCV occurs (21-23), possibly because mutated viruses have developed adaptations that allow them to proliferate in neural tissue (24). Hepatitis C is associated with altered cytokine profiles in CSF (20). Neurotropism and an altered immune response could possibly account for inflammation, leading to immune-mediated demyelination (25). Deposit of immune complexes on the myelin sheath or the cross-reaction of antibodies against myelin basic protein could impair myelin function (11). The minor elevation in serum ACE level was thought to be non-specific (26), as there were no clinical or radiological features to support the diagnosis of sarcoidosis.

We reject multiple sclerosis as the explanation for the optic neuritis in our patient because the optic neuritis was simultaneously bilateral and unassociated with demyelinating white matter lesions on MRI or CSF changes compatible with multiple sclerosis. Treatment of hepatitis C may cause bilateral anterior ischemic neuropathy (27,28), retinal artery or vein occlusion (29-32), macular edema, or nonmacular retinopathy at any time in the course in interferon therapy (33-37). The most frequent abnormalities are cotton wool spots and retinal hemorrhages (36,38,39) with a higher incidence in patients with concurrent hypertension (40) or diabetes (41). We do not think that treatment of hepatitis C played a role in our patient because it was started after her optic neuropathy had improved and there was continued recovery while she was receiving treatment.

Acknowledgment

We thank Dr. Jamie Weydert for interpretation of the liver pathologic samples.

REFERENCES


Optic Neuritis After Klebsiella Pneumonitis and Liver Abscess

Hyeon-Seok Lee, MD, Kwang-Dong Choi, MD, Ji-Eun Lee, MD, and Hye-Kyung Park, MD

Abstract: A 56-year-old woman developed a left optic neuropathy in the context of a Klebsiella pneumonitis that had also produced a liver abscess. Ophthalmic examination was normal apart from no light perception vision in the left eye and a left afferent pupil defect. Orbit and brain MRI revealed enhancement of the left optic nerve and several round enhancing areas in the gray-white junction of the frontal and temporal lobes consistent with micro-abscesses. Although the patient recovered systemically with antiinfective and corticosteroid treatment, she retained no light perception vision in the left eye 4 months later. The association of Klebsiella pneumonitis and optic neuritis has not been described previously. We presume that the organisms spread hematogenously.


Klebsiella pneumonitis can lead to endophthalmitis, especially in patients who also have pyogenic liver abscess or diabetes (1–4). We report a patient who developed optic neuritis without evidence of endophthalmitis in the setting of Klebsiella pneumonitis, liver abscess, and cerebral microabscesses, a clinical circumstance not described previously.

CASE REPORT

A 56-year-old woman was admitted to the internal medicine service in our hospital with a 1-week history of fever, dyspnea, and cough followed by depressed mentation. Her previous medical history had been unremarkable.

She had a body temperature of 38.5°C and a pulse rate of 90 beats/min. The white blood cell count was 15,600 cells/mm³ with 90% neutrophils. The aspartate aminotransferase level was 175 IU/L, and the alanine aminotransferase level was 168 IU/L. Chest x-ray showed patches of infiltration in the right lower lung field. CT of the abdomen revealed signal abnormalities consistent with a pyogenic liver abscess (Fig. 1). Blood cultures documented Klebsiella pneumoniae infection.

After administration of intravenous ceftriaxone and moxifloxacin for 20 days, she became alert and reported poor vision in her left eye. Visual acuity was 20/20 in the right eye and no light perception in the left eye. Visual fields to finger confrontation were normal in the right eye. Pupils were equal in size in dim illumination, but there was a left afferent pupil defect. The range of extraocular movements was full, and there was no ptosis, exophthalmos, or conjunctival injection. There was no evidence of anterior or posterior chamber inflammation on portable slit-lamp examination. Findings on ophthalmoscopy were unremarkable.

Postcontrast T1 MRI of the orbit and brain, performed 3 weeks after hospital admission, revealed...
FIG. 2. MRI performed 3 weeks after hospital admission. Postcontrast T1 axial (A) and coronal (B) MRI of the orbit shows enhancement of the orbital segment of the left optic nerve (white arrows). Postcontrast coronal MRI sections of the brain (C–D) show small round areas of enhancement at the cerebral gray-white junction consistent with microabscesses in the left frontal lobe (C, arrow) and temporal lobe (D, arrow).

enhancement of the left optic nerve (Fig. 2A–B) and small round areas of enhancement in the left frontal and temporal lobes consistent with microabscesses (Fig. 2C–D). Lumbar puncture showed a normal opening pressure, cell count, protein level, and glucose level with a negative bacterial culture.

Although the patient received 20 mg/day dexamethasone intravenously followed by oral prednisolone, examination 4 months later showed no recovery of visual function. Ophthalmoscopy revealed left optic disc pallor. The patient recovered completely from all other aspects of her infection.

DISCUSSION

The most common ophthalmic complication of K. pneumoniae infection is endophthalmitis (1–4). Our patient did not have any apparent ophthalmic complications except unilateral optic neuritis.

Paranasal sinuses and meningeal inflammation are potential routes of optic nerve infection in association with K. pneumoniae infection, but brain imaging in our patient did not show any abnormalities in the paranasal sinuses, and no meningeal inflammation was seen on the cerebrospinal fluid study (admittedly performed late in her clinical course). Considering the presence of microabscesses in the left frontal and temporal lobes and the pyogenic liver abscess, we presume that hematogenous spread is the likely underlying mechanism of optic neuritis in our patient.

REFERENCES

Ocular Neuromyotonia After Gamma Knife Stereotactic Radiation Therapy

Jason W. Much, MD, Eric D. Weber, MD, and Steven A. Newman, MD

Abstract: Three patients who underwent multiple intracranial operations for recurrent nonsecreting pituitary adenomas followed by gamma knife stereotactic radiosurgery developed diplopia at 1, 5, and 6 years after the treatments. Examination disclosed features of ocular neuromyotonia, a phenomenon attributed to radiation damage to ocular motor cranial nerves. Amply reported after external beam radiotherapy, neuromyotonia has not been described after radiosurgery previously. These patients are, however, exceptional in that all had undergone multiple sellar region operations or received high doses of radiotherapy, or both.

CASE REPORTS

Case 1
A 36-year-old woman with Cushing disease underwent subtotal transsphenoidal pituitary surgery because of persistent endocrine abnormalities. The following year she received 22-Gy gamma knife radiation for residual tumor close to the left optic nerve.

Because hormone levels remained abnormally high after this treatment, she underwent an additional 35.7-Gy gamma knife treatment 1 year later. Six years later, she developed diplopia and received a diagnosis of a left third cranial nerve palsy elsewhere. Because of the imaging disclosure of recurrent tumor, she underwent a second transsphenoidal operation. Several weeks after surgery, she complained that her left eye “would get stuck sometimes.”

On our examination, she displayed mildly reduced abduction of the left eye with sustained abduction after prolonged left gaze (Fig. 1). We made a diagnosis of partial left sixth cranial nerve palsy with ocular neuromyotonia and started therapy with 100 mg carbamazepine 3 times daily. On follow-up examination 6 months after starting carbamazepine treatment, she stated that the eye had stopped “getting stuck” 1 week after starting the drug. She reported no side effects. No ocular myotonia could be elicited on examination. She continued the carbamazepine at the same dose.

Case 2
A 27-year-old woman presented to her ophthalmologist complaining of blurred vision in the left eye. Brain MRI revealed an extensive sellar mass. She underwent subtotal resection of a nonsecreting pituitary adenoma via...
craniotomy and subsequently developed double vision. Six months later, a transsphenoidal resection was performed for residual tumor, but the diplopia persisted, and she was referred to us for evaluation.

On our examination 4 months after the transsphenoidal surgery, she had a right sixth cranial nerve palsy and a subtle left optic neuropathy. Three months after this visit, she received 50-Gy gamma knife radiation for residual tumor.

About 1 year after the gamma knife treatment, she complained of intermittent diplopia and reported that her right eye would “lock in” when she looked leftward. Our examination showed persistent exodeviation after prolonged right lateral gaze (Fig. 2). We diagnosed ocular neuromyotonia of the right sixth cranial nerve and treated her with 100 mg carbamazepine 3 times daily.

She discontinued the carbamazepine after 1 month because she did not think it was helping. We suggested an increased dose, but she declined it. She used no medication for the neuromyotonia. At a follow-up examination 3 months later, she reported decreased frequency of the eye “sticking,” and we found no evidence of ocular neuromyotonia.

Case 3

A 35-year-old woman had undergone two transsphenoidal resections and a craniotomy for a large, recurrent nonsecreting pituitary macroadenoma with growth into the left cavernous sinus. Two years after the craniotomy, she had received 58 Gy of external beam x-ray therapy, followed by 16-Gy gamma knife radiation 2 years later.

One year after the gamma knife treatment, she received the diagnosis elsewhere of an incomplete left third cranial nerve palsy with aberrant regeneration, which had been stable for more than 2 years until she began to notice worsening of diplopia. She underwent a lateral rectus recession and medial rectus resection on the left eye for...
exotropia. One year after the eye muscle surgery, she began to complain of her left eye “sticking in.”

On our examination, she demonstrated an exodeviation that changed to a transient esodeviation after sustained right gaze. We diagnosed ocular neuromyotonia of the left third cranial nerve and treated her with 100 mg carbamazepine 3 times daily, the patient stated that her symptoms of “eye sticking” had improved. In a telephone follow-up 1 year later, she reported that she had stopped using the carbamazepine because it “made my left eyelid droop more.” Although the drug relieved her myotonia, “the side effect was worse.”

DISCUSSION

We have reported three patients who developed ocular neuromyotonia at 1 year (Case 2), 5 years (Case 3), and 6 years (Case 1) after gamma knife stereotactic radiosurgery to the sellar/cavernous sinus region. Although ocular neuromyotonia has been amply reported after external beam irradiation (1–6), it has not been described after stereotactic gamma knife radiotherapy, which delivers a more precise, targeted dose of radiation over a single session. Admittedly, our patients are exceptional in that all required multiple sellar region operations and received either multiple doses of stereotactic radiosurgery (Case 1) or stereotactic and external beam radiation treatments for recurrent tumor (Case 3).

We present these patients to emphasize that neuromyotonia can occur after radiosurgery and that its clinical manifestations may be mistakenly attributed to cranial nerve palsy caused by recurrent tumor. Previous reports have established that ocular neuromyotonia is clearly a form of radiation-induced ocular motor cranial neuropathy (1–6). The standard treatment of ocular neuromyotonia has been oral carbamazepine, an agent known to reduce
neuronal and axonal excitability (9,10). Its efficacy in this condition is based purely on anecdote. Our experience with these patients does not allow us to be certain that it worked, and 2 of our patients discontinued its use because of perceived lack of benefit (Case 2) or side effects (Case 3).

REFERENCES
Intracranial Meningiomatosis Causing Foster Kennedy Syndrome by Unilateral Optic Nerve Compression and Blockage of the Superior Sagittal Sinus

X. Acebes, MD, J. Arruga, MD, PhD, J. J. Acebes, MD, PhD, C. Majos, MD, PhD, S. Muñoz, MD, and Isaac Alarcon Valero, MD

Abstract: The original description of the Foster Kennedy syndrome included the clinical triad of optic disc pallor in one eye, optic disc edema in the other eye, and reduced olfaction caused by space-occupying anterior fossa masses. The optic disc pallor was attributed to direct compression of the intracranial optic nerve, the optic disc edema to increased intracranial pressure from mass effect, and the reduced olfaction to direct compression of the olfactory nerve. We report a patient with the ophthalmic features of the Foster Kennedy syndrome from meningeal compression. A meningioma compressed one optic nerve to cause impaired visual function. Convexity meningiomas compressed the superior sagittal sinus to impair cerebral venous drainage, increased intracranial pressure, and papilledema in the other eye. This is the first report of the Foster Kennedy syndrome caused by this mechanism.


The original 1911 description of the Foster Kennedy syndrome included the triad of optic disc pallor in one eye, optic disc edema in the fellow eye, and anosmia or hyposmia in association with anterior cranial fossa mass lesions (1,2). The pathogenesis of the optic disc pallor was believed to be direct compression of the prechiasmatic optic nerve. The optic disc edema in the fellow eye was attributed to increased intracranial pressure from the space-occupying mass. The subnormal sense of smell was ascribed to direct compression of the olfactory nerve.

FIG. 1. Fundus photography performed at our initial examination shows optic disc pallor in the right eye and optic disc edema in the left eye.

Subsequently, other mechanisms have been proposed for this eponymous syndrome (3), including 1) direct but asymmetric compression of both optic nerves, with severe compression causing pallor, and less severe compression...
causing optic disc edema owing to impaired axoplasmic flow; and 2) chronic increased intracranial pressure initially causing bilateral papilledema, with one optic disc eventually developing pallor as the result of axonal death and the other optic disc remaining swollen. In previously reported cases of this syndrome, the increased intracranial pressure has been caused either by a space-occupying mass or by blockage of cerebrospinal outflow (3).

We present an example of the Foster Kennedy syndrome in which meningiomatosis caused direct compression of one optic nerve (and ipsilateral optic disc pallor) and increased intracranial pressure from blockage of the dural venous sinus outflow (and fellow eye papilledema).

**CASE REPORT**

A 33-year-old woman with neurofibromatosis type 2 underwent surgery for bilateral vestibular acoustic schwannomas and for a foramen magnum astrocytoma. She had been aware of long-standing subnormal vision in her right eye (without medical explanation) but had had no difficulties with the vision in her left eye.

Eight years after the intracranial surgery, she noticed declining vision in both eyes, but particularly in her left eye. She denied other neuro-ophthalmic symptoms.

On our examination, visual acuity was light perception in the right eye and 20/30 in the left eye. A right relative afferent pupillary defect was present.

**FIG. 3.** MRI performed at the time of our initial examination. **A.** Postcontrast T1 sagittal image shows multiple lesions occupying the superior sagittal sinus and posterior fossa. **B.** Postcontrast T1 axial image shows a mass around the anterior clinoid process (black arrow), intracanalicular right optic nerve, and anterior aspect of the chiasm (white arrows). There is also an intraorbital mass affecting the right medial rectus muscle (asterisk). **C.** Postcontrast T1 coronal image shows that the prechiasmal right optic nerve is surrounded by meningioma (arrow). **D.** Coronal short time inversion recovery (STIR) image shows that the prechiasmatic right optic nerve, hypointense in this sequence, is compressed by meningioma (black arrow).
No relevant biomicroscopic findings were present, and on ophthalmoscopy optic disc pallor was present in the right eye and optic disc edema was present in the left eye (Fig. 1). Humphrey perimetry of the left eye disclosed an inferior nerve fiber bundle defect (Fig. 2). Neurologic examination revealed residual bilateral facial palsy with lagophthalmos but was otherwise unremarkable.

MRI of the brain and orbits (Fig. 3) showed multiple supratentorial and infratentorial meningeal-based masses that strongly enhanced, consistent with the diagnosis of meningiomatosis. Meningiomas extensively involved the brain convexity, particularly the superior sagittal sinus (Fig. 3A). One of the meningiomas extended from the right orbital apex through the optic canal and into the intracranial space (Fig. 4B–D). Bilateral acoustic masses were also present.

We diagnosed compressive optic neuropathy of the right eye and papilledema of the left eye due to impaired venous drainage in the superior sagittal sinus. To treat the increased intracranial pressure, we prescribed 250 mg acetazolamide QID and placed a ventriculoperitoneal shunt.

Over the ensuing 20 months, visual acuity improved in the right eye from light perception to 20/400 and remained 20/30 in the left eye. The papilledema in the left eye had resolved after 5 months, and the visual field defect in the left eye had improved slightly (Fig. 4). The acetazolamide treatment was discontinued at 5 months.

The patient’s ophthalmic status has remained stable for 20 months and there have been no complications from the shunt.

DISCUSSION

We have described a patient who developed the ophthalmic manifestations of the Foster Kennedy syndrome—optic disc pallor in one eye and optic disc edema in the other eye—from a meningioma compressing one optic nerve (to produce optic disc pallor) and another meningioma compressing the superior sagittal sinus and causing increased intracranial pressure from impaired dural venous sinus drainage (to produce papilledema). We believe that this mechanism has not been described previously as underlying these ophthalmic manifestations.

Meningiomas arising from the anterior third of the falx cerebri or in the subfrontal region, as Foster Kennedy described (1), may become quite large before they are discovered. By that time, the most common signs and symptoms are caused by long-standing increased intracranial pressure from mass effect (4). Such patients complain of headache or they display deterioration of mental function (5).

Our patient differs from these reported cases in that the increased intracranial pressure was caused by impaired dural venous sinus drainage. The importance of this observation is that treatment does not involve tumor removal but rather lowering of intracranial pressure, first with acetazolamide and definitively with cerebrospinal fluid diversion. In our patient, visual function apparently improved not only in the eye with papilledema but also in the eye whose optic nerve was being compressed by meningioma, indicating that a component of visual loss in that eye probably also came from increased intracranial pressure.

We emphasize that prompt cerebrospinal fluid diversion is critical in preventing visual loss in this setting even though the brain ventricles are typically of normal size.

REFERENCES


FIG. 4. Visual field examination performed 5 months after placement of the ventriculoperitoneal shunt shows slight improvement in the defect relative to Fig. 2.
Increased Anti-saccade Latency Is an Isolated Lingering Abnormality in Sydenham Chorea

Sheree Cairney, PhD, Paul Maruff, PhD, Jon Currie, FRACP, and Bart J. Currie, FRACP

Abstract: Sydenham chorea (SC) is an autoimmune response to group A β-hemolytic streptococcal infection whose clinical and imaging manifestations usually resolve within 6 months. We used ocular motor analysis and neuropsychologic assessment to investigate residual striatal dysfunction in two individuals with histories of childhood SC whose most recent episodes of chorea had occurred 5 and 17 years before testing. Compared with the performance of 33 age-matched control subjects, both SC subjects showed significantly increased anti-saccade latencies. These findings support recent theories that acute episodes of SC may cause long-term corticostriatal changes in some individuals.


As an expression of rheumatic fever, Sydenham chorea (SC) is an autoimmune response to group A β-hemolytic streptococcal infection characterized by severe impairment in psychomotor function with involuntary movements, muscle weakness, and emotional lability (1). The manifestations of SC usually subside spontaneously within 2–6 months of an acute episode (1). A more persistent form of SC has been reported with manifestations continuing beyond 2 years (2), but complete recovery from chorea does occur eventually. Recurrent episodes of SC are most likely to occur within the 2 years after a previous episode of SC, but in some individuals an increased susceptibility to further episodes continues into adulthood (3).

Striatal abnormalities are consistently implicated as the origin of SC on the basis of behavioral characteristics and neuroimaging (2). Whereas neuroimaging studies and behavioral observations generally affirm complete resolution (2), there is evidence of permanent striatal dysfunction after an acute episode of SC. For example, some individuals with a history of SC maintain an increased susceptibility to dopaminergic agents and to recurrent episodes of chorea that may continue throughout their lives (3). The episodes have been stimulated by pregnancy (chorea gravidarum), oral contraceptive treatment, and senescence. For some individuals, an acute episode of SC may produce irreversible changes in the basal ganglia and thereby a subsequent long-term susceptibility to recurrent episodes of chorea (3).

To investigate residual neurologic dysfunction long after SC occurring in childhood and adolescence, we examined ocular motor indicators and neuropsychologic parameters in two individuals with a history of acute rheumatic fever and SC and compared their results to those of a matched healthy control group of 33 individuals.

CASE STUDY

Subjects

For the two SC subjects, diagnosis was based on the 1992 updated Jones criteria (4) and confirmed from clinical notes and hospital admission data. Other causes of chorea were excluded. At the time of testing, these individuals showed no chorea and no neuropsychiatric symptoms. Their most recent episodes had been 5 and 17 years earlier. All subjects had been enrolled in a large study of substance abuse in remote Aboriginal communities in northern Australia (5,6), but neither the SC subjects nor the members of the healthy control group had histories of substance abuse or psychiatric illness. The study was approved by the relevant institutional ethics committees with input from an Aboriginal subcommittee. All subjects...
gave written informed consent to participate before the assessment procedure.

Procedure

The ocular motor and neuropsychologic tests used here are identical to those used in our previous studies based on Aboriginal Australians living in remote communities and have been described in detail in earlier publications (5,6). Ocular motor recordings were performed in a darkened room with the head stabilized, using a high-resolution infrared scleral reflectance technique (IRIS, Skalar; bandwidth DC to 100 Hz [23 dB]). Participants were seated 1 m from a horizontal display of light-emitting diode (LED) (16.9 cd/m²; rise time 3 ms) visual targets with computer-controlled illumination timing. Eye and target position signals were digitized at 1 kHz and scored for off-line computer analysis. Eye position was differentiated using a computer-based algorithm to obtain eye velocity. Subjects were required to make visually guided reflexive eye movements (saccades) to fixate random targets moving with unpredictable direction, amplitude (615), and timing (range 1.5–2.5 s).

For each subject, the initial saccade was scored as hypometric if it attained less than 85% of the target step and hypermetric if it attained more than 115% of the target step. Anticipatory saccades were defined as saccades made before or less than 70 ms after target appearance (7). Saccade latency was calculated as the duration from the onset of the target to the onset of the saccade, and saccade accuracy was calculated as the displacement of the final eye position with respect to the target position. The duration and peak velocity for visually guided saccades were plotted against saccade amplitude.

The anti-saccade task involved making voluntary saccades to fixate a central green LED (16.9 cd/m²) target that was offset simultaneously with the appearance of a peripheral red target at either 610 or 615. Subjects were instructed to inhibit a reflexive saccade to the peripheral red target and instead to generate an anti-saccade to its mirror location and hold fixation until the green LED reappeared in the center. Displacement and timing (3.0–3.5 seconds after fixation) of the appearance of the peripheral red target was random. A correct anti-saccade response was an initial eye movement away from the midline to the side opposite to that of the peripheral red target. Any initial reflexive eye movement toward the target was scored as incorrect even if a subsequent correction to the opposite side was made. The latency for the onset of correct anti-saccades was recorded and a percent error rate was calculated.

Neuropsychologic tests were drawn from the touch screen-based Cambridge Automated Neuropsychological Test Battery (CANTAB). The selected assessment battery included tasks of psychomotor speed, recognition memory, and paired-associate learning. More detail on these assessments and the experimental setup is available elsewhere (6,8).

Data Analysis

Demographic, ocular motor, and neuropsychologic data for patients with SC were compared against confidence intervals derived from control data based on 1.96 standard deviations from the group mean. Before analysis, the distributions of data for each performance measure were inspected for normality and heterogeneity of variance. Where data did not meet the assumptions for parametric statistics, the distributions of scores were transformed. Accuracy measures on the recognition memory task that were scored as percent correct formed negatively skewed distributions, and arcsine transformations were used to normalize these distributions.

RESULTS

All data for patients and control subjects are presented in Table 1. In comparison with control data, both SC subjects showed no sign of dysmetria or anticipatory saccades and normal performance for saccadic duration, saccade peak velocity, anti-saccade errors, paired associate learning, and recognition memory. On the anti-saccade task, both patients with SC showed normal error rates but significantly elevated latencies to perform correct anti-saccades.

DISCUSSION

The two individuals who had had episodes of SC 5 and 17 years earlier showed significantly increased latencies in the initiation of anti-saccades, evidence of lingering corticostriatal dysfunction. They had no dysmetria or saccadic disinhibition, as judged by the normal anti-saccade error rates and no deficits in recognition memory or paired-associate learning.

Increased anti-saccade latency in combination with normal anti-saccade error rates have been observed in patients with lesions of the frontal eye fields (FEFs) and in individuals with Tourette syndrome, which affects the basal ganglia (9,10). Neuroimaging studies and neuronal studies in primates have further validated the importance of neural networks that involve cortical and basal ganglia brain regions for triggering voluntary saccades (9). Thus, the pattern of ocular motor performance observed here among individuals with a history of SC is observed typically when corticostriatal pathways are disrupted. These data therefore provide evidence of residual striatal dysfunction after SC.

Our findings of ocular motor abnormalities many years after the manifestations of acute SC have subsided may reflect the benefit of specific functional investigation enabled through ocular motor analysis. However, these
TABLE 1. Demographics and neuropsychologic and ocular motor performance measures for two subjects with a history of Sydenham chorea and 33 healthy control subjects

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control subjects (n = 33)</th>
<th>SC1</th>
<th>SC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.3 (5.4)</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Sex</td>
<td>M (n = 33)</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>No. episodes chorea</td>
<td>N/A</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Age first episode (years)</td>
<td>N/A</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Time since most recent episode (years)</td>
<td>N/A</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>734 (285)</td>
<td>896</td>
<td>997</td>
</tr>
<tr>
<td>Recognition memory (arcsine % correct)</td>
<td>0.99 (0.26)</td>
<td>0.91</td>
<td>0.84</td>
</tr>
<tr>
<td>Paired associate learning (total number of errors)</td>
<td>24.5 (16.7)</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>No. hypometric saccades</td>
<td>18.6 (14.1)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No. hypermetric saccades</td>
<td>10.2 (17.5)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>No. anticipatory saccades</td>
<td>9.6 (10.8)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Reflexive saccades:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>170.0 (23.3)</td>
<td>173.5 (46.5)</td>
<td>188.2 (37.1)</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>98.8 (12.74)</td>
<td>100.9 (9.6)</td>
<td>97.4 (6.8)</td>
</tr>
<tr>
<td>Peak velocity (coefficient of variation)</td>
<td>146.8 (31.7)</td>
<td>201.0</td>
<td>133.4</td>
</tr>
<tr>
<td>Duration (amplitude gradient)</td>
<td>2.16 (0.43)</td>
<td>2.20</td>
<td>2.17</td>
</tr>
<tr>
<td>Anti-saccades:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error rate (%)</td>
<td>16.3 (12.4)</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>260.9 (38.8)</td>
<td>372.9 (91.4)*</td>
<td>373.5 (76.2)*</td>
</tr>
</tbody>
</table>

Control data are presented as group mean (SD).
*Values fall outside confidence intervals based on control data (mean ± 1.96 SD).
F, female; M, male; N/A, not applicable; SC, Sydenham chorea; SC1, first patient with SC; SC2, second patient with SC.

Acknowledgments
We gratefully acknowledge the Aboriginal health workers and clinic staff from the communities involved.

REFERENCES
Ipsilateral Wallerian Degeneration of the Distal Optic Radiations After Infarction at Their Root

Mi Young Oh, MD, Jeong-Min Hwang, MD, Yun Joong Kim, MD, and Ji Soo Kim, MD

FIG. 1. A. Axial T2 MRI at two levels discloses a round high signal area involving the root of the right optic radiations (arrow) and a strip of high signal running along the ipsilateral optic radiations in their course toward the striate cortex (arrowheads). These findings are consistent with infarction of the proximal optic radiations, perhaps from occlusion of the anterior choroidal artery, and Wallerian degeneration of the more distal optic radiations. B. Visual field examination demonstrates a left homonymous inferior quadrantanopia corresponding to the right optic radiation signal abnormality.
Abstract: A 54-year-old man who developed a left homonymous inferior quadrantanopia showed MRI findings of infarction of the proximal portion of the right superior optic radiations and high T2 signal along the entire distal course of the ipsilateral optic radiations consistent with Wallerian degeneration. Frequently reported in other settings, this imaging abnormality has rarely been described in anterior optic radiation lesions.


A 54-year-old man was found to have a left homonymous inferior quadrantanopia during evaluation of the complaint of blurred vision present for several months. He had essential hypertension treated with antihypertensive medication. Results of a review of his systems were negative.

Brain MRI, performed 4 months after the initial detection of the visual field loss, revealed features consistent with infarction of the right proximal portion of the optic radiations near the lateral geniculate body, and ipsilateral Wallerian degeneration of the optic radiations extending posteriorly to the striate (primary visual and calcarine) cortex (Fig. 1A).

Our examination confirmed the visual field defects (Fig. 1B) with normal visual acuity, color vision, ocular motility and alignment, pupillary size and reactivity, and ophthalmoscopy. The neurologic examination was otherwise normal.

The optic radiations connect the lateral geniculate body with the ipsilateral striate cortex (Fig. 2). The radiation fibers conveying visual information for the superior visual field quadrants sweep around the temporal horn of the lateral ventricle to form Meyer’s loop. The fibers serving the inferior visual field quadrants course directly backward to the striate cortex (1). The fact that the visual field defect in our patient was mostly confined to the left inferior quadrant indicates damage to the superior portion of the optic radiations, possibly due to occlusion of the anterior choroidal artery (2).

Wallerian degeneration refers to antegrade distal degeneration of the axon and its myelin sheath resulting from damage to the proximal portion of the axon itself or its cell body (3). Wallerian degeneration becomes evident on T2 MRI as a hypointense signal usually 4 weeks after infarction and turns into a hyperintense signal 6–10 weeks later (3). Diffusion imaging may detect Wallerian degeneration earlier than T2 MRI (4,5).

FIG. 2. Location of the lateral geniculate body (curved arrow) and optic radiations (straight arrow) in the corresponding axial slices of a normal brain.
Wallerian degeneration has been reported on MRI in various diseases (6,7), but most often in patients with stroke involving the corticospinal tract (3,8). In contrast, reports on Wallerian degeneration of the optic radiations have been sparse (9,10). It was first described in a single report describing a patient with an arteriovenous malformation and a patient with metastatic sarcoma involving the lateral geniculate body (9). A T2 hyperintense layer was observed in the external sagittal striatum in another patient with an old infarction extending from the lateral geniculate body to the occipital lobe (10). Although mentioned in the reports, the visual field defects were not displayed in those reports (9,10).

This is the first documentation of visual field defects associated with Wallerian degeneration of the optic radiations in a patient with presumed stroke involving the proximal portion of the optic radiations. More careful scrutiny of MRI studies may disclose this finding.

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Abstract: A 65-year-old man with a 3-year history of difficulty seeing had normal ophthalmologic and neurologic examinations except for impaired visual spatial and perceptual function. Brain MRI failed to disclose any structural abnormalities, but positron emission tomography (PET) performed 2 weeks later showed prominent hypometabolism in the parieto-occipital regions bilaterally. These findings were considered consistent with the visual variant of Alzheimer disease (VVAD). Although the dissociation between normal structural and abnormal functional imaging has been reported before in VVAD, this patient is a reminder that PET may be useful to confirm the diagnosis before the disease becomes advanced.

FIG. 1. A. Axial FLAIR MRI (in ascending sections from left to right) in our patient shows no obvious atrophy. B. Positron emission tomography (PET) using 2-[18F]fluorodeoxyglucose, performed 2 weeks later, shows hypometabolism in the parieto-occipital regions bilaterally (arrowheads). C. PET of age-matched and sex-matched control subject shows normal metabolism in those regions. (Red, yellow, green, and blue represent a decreasing scale of glucose metabolism.)
A 65-year-old man with a master’s degree reported difficulty seeing and reading that had begun 3 years earlier. Ophthalmologic examination was normal. Neurologic examination was remarkable only for a score of 26 of 30 points on the Mini-Mental Status Examination and slow reading with poor comprehension. Formal neuropsychometric testing confirmed borderline impaired cognitive function with a predominant deficit in visual perceptual and visual spatial processing.

Brain MRI (Fig. 1A) was normal. Results of other ancillary studies, including carotid Doppler ultrasonography, complete blood count, routine blood chemistry analyses, rapid plasma reagin (RPR) serology, thyroid function tests, and vitamin B₁₂, were also normal.

PET performed 2 weeks after the brain MRI study showed prominent hypometabolism in the parieto-occipital region bilaterally (Fig. 1B), moderate hypometabolism in temporoparietal regions, and normal metabolism in the posterior cingulate region, as compared to a normal control study (Fig. 1C). These findings were considered characteristic of the visual variant of Alzheimer disease (VVAD).

Our patient with VVAD is noteworthy because brain MRI failed to disclose brain atrophy. Correlation with the visual perceptual and spatial dysfunction found on clinical testing was found only with posterior hemispheric hypometabolism on PET.

One study of patients with other variants of dementia showed an 83% sensitivity and 85% specificity for Alzheimer disease using a visual rating scale for temporal lobe atrophy (1). Quantitative MRI studies with serial volume measurement might be more sensitive, but because of lack of automation and their labor-intensive nature, they have limited usefulness in clinical practice (2).

PET using 2-[¹⁸F]fluorodeoxyglucose has proven diagnostic value in VVAD with hypometabolism seen before structural imaging discloses atrophy (3).

In VVAD, visual manifestations may precede memory and cognitive impairment by years, leading sometimes to a misdiagnosis of psychogenic visual loss (4,5). Alexia, visual spatial dysfunction, the inability to interpret complex scene (simultanagnosia), difficulty recognizing familiar objects (visual agnosia), and sometimes visual field defects are features of VVAD (4,6). Visual spatial tests, such as drawing a clockface, copying the Rey diagram, and interpreting pictures, can bring out deficits not readily recognized in the standard ophthalmic or neurologic examinations.

Interestingly, our patient became claustrophobic in the magnetic resonance scanner, and three attempts to perform MRI failed despite increasing oral sedation before successful completion with general anesthesia. Others (6) have noted a higher dropout rate among VVAD study patients than among those with other variants of dementia because of failure to complete the imaging portion of the protocol (6). This excessive claustrophobia may be due to disintegration of a coherent representation of visual space.

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“Ophthalmoplegic Migraine” With Reversible MRI Enhancement of the Cisternal Sixth Cranial Nerve

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Abstract: A 45-year-old woman reported multiple episodes of reversible left eye pain and diplopia stretching over 12 years. Ophthalmic examinations had repeatedly disclosed a left sixth cranial nerve palsy. Postcontrast brain MRI performed 3 weeks after clinical onset of the most recent episode demonstrated enhancement of the cisternal segment of the left sixth cranial nerve. Five months later, when symptoms and signs had largely abated, postcontrast brain MRI was normal. The clinical diagnosis satisfies the criteria for “ophthalmoplegic migraine.” Although reversible cisternal enhancement of the third cranial nerve has been often described in this condition, this is the first report of cisternal enhancement of the sixth cranial nerve.

A 45-year-old woman had episodic severe left eye pain and double vision for 12 years. The episodes occurred 2–3 times per year and symptoms usually lasted about 4 weeks. Each episode started abruptly with steady left periocular pain (rated 8 of 10 in severity) that often awakened her from sleep. She reported photophobia and phonophobia but no obvious pupil size changes, tearing, or nasal discharge. The pain usually abated a few hours after she received parenteral ketorolac, meperidine, or corticosteroids. After receiving treatment, she usually slept but always awoke to binocular diplopia that was horizontal and worse at distance and on left gaze. The pain never lasted for more than 2 or 3 days, but the diplopia usually lasted for at least 4 weeks.

Propranolol, topiramate, and indomethacin did not prevent the attacks. Abortive agents, including nonprescription medications and triptans, neither helped the headaches nor prevented the diplopia. She had a history of depression, hypertension, two cesarean deliveries, an appendectomy, and a fractured elbow. Her medications were valsartan, metoprolol, alprazolam, a daily vitamin, and topiramate (50 mg daily).

At the time of our first examination, the patient reported a typical episode starting 3 months earlier, with diplopia that was initially present in the primary gaze position and gradually improved so that it was present on left gaze. Visual acuity was 20/20 in each eye at distance and near viewing. Her eyes were aligned in primary position but she had only 75% abduction of the left eye. The right pupil was fractionally larger than the left, but both reacted briskly to light and near stimuli. The palpebral fissures were equal in height. The ophthalmologic and neurologic examinations were otherwise normal. When examined 2 months later, 5 months after the onset of the current episode, she had diplopia only on extreme left gaze and 90% abduction of the left eye.

Brain and orbit MRI, which was performed 3 weeks after the onset of the current episode, demonstrated enhancement of the left sixth cranial nerve in the pre-pontine cistern (Fig. 1A–C). Brain MRA showed no abnormality. A second brain MRI (Fig. 1D), performed 5 months after the commencement of the current episode, demonstrated no sixth cranial nerve enhancement.

“Ophthalmoplegic migraine” (OM), a rare enigmatic disorder with an annual incidence of about 1 per million (1), was reclassified by the International Classification of Headache Disorders, 2nd ed. (ICHD-III) (2) as a recurrent neuralgia under the category “cranial neuralgias and central causes of facial pain.” The onset of OM is usually, but not always, in the first decade. Involvement of the third cranial nerve is more common than involvement of the fourth or sixth cranial nerves, and simultaneous impairment of more than one ocular motor nerve is exceptional (1).

Many patients with OM clinically involving the third cranial nerve demonstrate enhancement or thickening, or both, of the cisternal segment of the third cranial nerve (3,4) that is usually reversible within 7–9 weeks (3) (Fig. 2). Isolated enhancement of the fourth cranial nerve has been reported once in this condition (5) (Fig. 3). There has also been one previous report of reversible enhancement of the intraparenchymal portion of the sixth cranial nerve in OM (Fig. 4) (6), but no previous report of enhancement of the...
cisternal portion of the sixth cranial nerve such as we are describing here.

MRI enhancement of the cranial nerves occurs with infectious, inflammatory, demyelinating, and neoplastic disorders. Enhancement of the cisternal portion of the sixth cranial nerve is reported with trauma, ischemia, venous congestion associated with a medullary venous malformation, leukemia, chemical meningitis, the Fisher variant of acute inflammatory demyelinating polyneuropathy (AIDP), polyneuritis cranialis (probably a variant of AIDP), multiple sclerosis, diabetes mellitus, meningoencephalitis, autoimmune disorders such as the Tolosa-Hunt syndrome (7), Lyme disease (8), and vincristine therapy (9). This is the first report of enhancement of the cisternal portion of the sixth cranial nerve in OM.

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Cerebral Blindness After Scorpion Sting

A 40-year-old woman was stung by a scorpion on her left foot. Sharp burning pain at the bite site was followed by a high-grade fever, severe breathlessness, oliguria, and altered sensorium over a period of hours. She was rushed in an unconscious state to a critical care center where blood pressure was 90/60, and she was diagnosed with acute pulmonary edema, myo carditis, and acute renal failure (venom-induced multiorgan failure). After endotracheal intubation, she received low-dose aspirin, enalapril, and supplemental intravenous fluids.

Eight hours later, on recovery of consciousness, she reported poor vision in both eyes. On examination 1 week later, visual acuity was light perception in both eyes. Anterior segments were unremarkable, including pupillary reactions. A dilated fundus examination was normal in both eyes. Limb ataxia, dysdiadochokinesis, poor tandem walking, and staccato speech could be elicited. Otherwise the findings from neurological examination appeared to be normal.

Brain MRI revealed restricted diffusion in the medial occipital (Fig. 1) and occipitotemporal lobes and cerebellum bilaterally. Results of a coagulation profile, C3 and C4 complement, homocysteine, protein C and S, VDRL, antinuclear antibody (ANA), and antiphospholipid antibody were negative. Cerebrospinal fluid analysis and a color Doppler study of both carotid and vertebral arteries showed normal results.

A diagnosis of cerebral and cerebellar infarction was made. No direct treatment occurred. Over 10 days, there was gradual improvement so that the patient was able to walk without support. At the 6-month follow up, visual acuity was light perception in both eyes, the only neurologic deficit.

Scorpion bites affect the central nervous system in three ways: altered consciousness, seizures, and infarctions (1). Cerebral and/or cerebellar infarctions have been reported (2-7), with numerous mechanisms advanced to explain them: 1) an acute rise in blood pressure during the autonomic storm that ruptures unprotected or diseased vessels (2); 2) toxic myocarditis that precipitates arrhythmias that give rise to embolic stroke (2); 3) hypercoagulability (3); 4) disseminated intravascular coagulation (4); 5) vasculitis caused by venom (5); and 6) hypotension caused by myocarditis, parasympathetic overactivity, and dehydration (6).

Bilateral optic neuropathy (6), transient ophthal moplegia (8), transient blindness (9), and myelopathy (10) have been documented. We believe that this is the first description of persistent (and severe) cerebral visual loss after a scorpion bite. We cannot be certain of the mechanism, although hypotension seems likely.

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Letters to the Editor


Atypical Central Serous Chorioretinopathy With Peripapillary Subretinal Fluid Suggesting an Optic Neuropathy

I recently examined a patient with atypical features of central serous chorioretinopathy (CSC) (1) extending to the peripapillary region that mimicked the fundus findings of an optic neuropathy.

A 43-year-old man presented with distorted vision in his left eye noted upon awakening that morning. He described the area of distorted vision as being slightly temporal to the center of fixation. He denied recent illness, pain on eye movements, photophobia, constitutional symptoms, or injuries to the eye.

Past medical history was unremarkable. Past ocular history was significant for moderate myopia and a well-healed left upper lid laceration from a distant injury. He took no prescription medications, including no corticosteroid formulations, and only occasionally consumed alcohol or used tobacco products. Family history was noncontributory.

Uncorrected visual acuity was 20/20 in the right eye and 20/60 in the left eye. The patient had been emmetropic in the past. On this examination, visual acuity improved to 20/20 in the left eye with +1.25 sph, indicating a new hyperopic shift. Ishihara plates were correctly identified by both eyes. However, mild red desaturation was reported in the left eye. The patient reported mild micropsia with the left eye, and Amsler grid testing confirmed vertical metamorphopsia just temporal to fixation. Confrontation visual fields were full. Intraocular pressures were 16 mm Hg in both eyes. Pupils were of equal size and constricted briskly to direct light without a relative afferent pupil defect (RAPD). Extraocular movements and alignment were normal, as was biomicroscopic examination of the anterior ocular segment.

Ophthalmoscopy of the right eye disclosed faint retinal pigment epithelium (RPE) mottling within the fovea as the only abnormality. In the left eye, there were foveal pigmentary alterations and subretinal fluid. The optic disc margins were blurred without pallor or hemorrhage. There was circumferential subretinal fluid around the optic disc (Fig. 1A). OCT of the left macula and peripapillary region revealed fluid under the neurosensory retina (Fig. 1B). There was no retinal thickening.

Humphrey visual field 24-2 was normal in the right eye and revealed mild paracentral depression temporally in the left eye.

Fluorescein angiography in the left eye revealed four pinpoint foci of hyperfluorescence at the level of the RPE exhibiting increasing leakage through the later phases of the angiogram. The optic nerve margins were blurred but there was no hyperfluorescence or leakage from the optic disc. There was no pooling of dye within the subretinal space around the optic nerve (Fig. 2).

FIG. 1. Fundus photograph (A) of the left eye demonstrates optic nerve edema with a cuff of subretinal fluid surrounding the optic nerve. The macula demonstrates pigmentary alterations and evidence of subneurosensory fluid accumulation. A 6-mm horizontal optical coherence tomography (OCT) scan (B) demonstrates subretinal fluid adjacent to the optic nerve as well as in the macular region (asterisk).
encountered in optic neuropathy, may also be reported in CSC, as in this patient.

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Papilledema Caused by a Thoracic Schwannoma

Increased intracranial pressure rarely occurs with spinal tumors at any level but is most common with upper cervical tumors (1). There has been no report of papilledema attributed to a thoracic schwannoma.

A 54-year-old man had headaches and papilledema without other signs of nervous system dysfunction. Lumbar puncture revealed an opening pressure of 440 mm water, a protein level of 210 mg/dL, and a mild pleocytosis. Brain CT and MRI showed no abnormalities. Accordingly, we performed MRI of the spinal cord which disclosed a T2-3 intraspinal tumor (Fig. 1). Surgical removal disclosed a schwannoma. One month after the operation, there was no headache, papilledema, or neurologic deficit. The lumbar puncture was not repeated.

The five previously reported cases (2-6) of intraspinal schwannomas/neuromas and papilledema have included tumors of the cauda equina, cervical spine, and lumbar spine, but not thoracic spine.

Examination 2 months later was unchanged in the right eye. In the left eye, visual acuity had improved to 20/50, and the hyperopia and most of the subretinal fluid had disappeared. A creamy yellow-white subretinal lesion was now present immediately above the fovea.

My patient exhibited CSC with subretinal fluid around the optic disc, a rarely reported set of findings in CSC. There was no evidence of optic nerve dysfunction as color vision and pupillary reactions were normal. No optic pit or optic nerve head drusen (ONHD) were seen by ophthalmoscopy, OCT, or fluorescein angiography with autofluorescence.

Multiple simultaneous pinpoint leaks on fluorescein angiography are unusual in acute CSC but are not unusual in the chronic severe form of CSC called diffuse retinal pigment epitheliopathy. Although multiple pinpoint leaks can also occur in Harada disease, leukemic infiltration, hypertensive retinopathy, and various inflammatory conditions, but there was no clinical support for these entities in our patient.

Brodsky (2) described a single case labeled as central serous papillopathy. He proposed that the neurosensory detachment emanated from a discrete area of capillary leakage within a nonexcavated optic disc. Ours is an atypical case of CSC with submacular retinal edema and peripapillary edema that mimicked optic disc edema. Admitting that extension of subretinal fluid to the peripapillary area is unusual in CSC, the complaints of metamorphopsia and micropsia, in the absence of a relative afferent pupil defect, identified a retinal origin of this condition. The complaint of red desaturation, so often
The pathogenesis of intracranial pressure elevation caused by spinal schwannomas is uncertain. It has been suggested that they may secrete protein kinase, which evokes synthesis of increased protein or that the protein represents a tumor breakdown product that interferes with absorption of cerebrospinal fluid (CSF) (7). Venous stasis caused by tumor compression of spinal or medullary venous plexuses producing an unfavorable transarachnoid villous hydrostatic pressure is another proposed mechanism that could lead to transudation of substances and further elevation of protein (8).

Subarachnoid hemorrhage is described in about one-quarter of patients with spinal tumors and could be responsible for papilledema (9). Blockage of the CSF outflow by spinal arachnoid adhesions can also cause raised intracranial pressure (10). The spinal canal, acting as an elastic reservoir for CSF, is thought to be important in maintenance of a constant intracranial volume. By compromising this system, spinal tumors may reduce the capacity of this reservoir (11).

Comprehensive spine imaging should be a part of the evaluation of a patient with papilledema who has normal brain imaging, especially if spinal fluid protein is elevated and even if there are no clinical manifestations of a spinal tumor.

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Anterior Ischemic Optic Neuropathy After Strabismus Surgery

We report a case of nonarteritic anterior ischemic optic neuropathy (NAION) in a healthy young woman after strabismus surgery.

A 26-year-old woman with no medical history underwent uneventful left medial rectus recession and lateral rectus resection for a long-standing esotropia under general anesthesia. Preoperatively, visual acuity had been 20/20 in the right eye and 20/200 in the left eye (amblyopia). Thirteen days postoperatively, she noticed loss of vision superiorly in the left eye on awakening without any other symptoms.

On our examination the next day, visual acuity was 20/20 in the right eye and 20/400 in the left eye. She had a superior nerve fiber bundle (altitudinal) visual field defect on confrontation, a left relative afferent pupillary defect, and mild left optic disc swelling, mainly inferiorly (Fig. 1). The right optic disc had a normal appearance. Both discs had a cup-to-disc ratio of 0.1. All other aspects of the ophthalmic examination were normal.

Results of standard laboratory tests, including a full blood cell count, serum electrolytes, erythrocyte sedimentation rate, C-reactive protein, thyroid function, blood glucose, and anti-nuclear, anti-mitochondrial, anti-smooth muscle, and anti-parietal cell antibodies, were normal. MRI of the brain and orbits was unremarkable.

Four weeks later, visual acuity in the left eye had returned to its baseline level of 20/200, but the altitudinal

FIG. 1. Fundus photography performed 1 day after onset of visual field loss shows left optic disc swelling.
The optic neuropathy and strabismus surgery were necessarily related.

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**Transient Corneal Edema and Left Hemisphere Dysfunction in Pearson Syndrome**

Pearson syndrome is a rare mitochondrial disorder of infancy manifested by sideroblastic anemia, pancytopenia, exocrine pancreatic insufficiency, and variable involvement of the kidneys and liver (1). Large deletions in the mitochondrial genome lead to derangement of oxidative metabolism and a decreased mitochondrial energy supply (2). The neurologic manifestations include hypotonia, developmental delay, ataxia, and tremor (3). There are no reported ophthalmic findings. Patients who survive infancy may later develop Kearns-Sayre syndrome (KSS) (4).

Persistent corneal edema attributed to endothelial dysfunction has been reported in KSS (3,5,6) and in chronic progressive external ophthalmoplegia (CPEO) (7), but transient corneal edema has not been reported in any mitochondrial disorder. We recently examined a 3-year-old girl with Pearson syndrome who developed transient corneal edema in conjunction with transient left cerebral hemispheric dysfunction manifesting as left gaze deviation and right hemiparesis. Such phenomena have not been reported previously in Pearson syndrome.

Pearson syndrome was diagnosed in the patient at 12 months of age after she presented with transfusion-
dependent sideroblastic anemia. Testing revealed a large mitochondrial DNA deletion. She later developed pancreatic insufficiency and Fanconi renal disease.

At 3 years and 9 months of age she was admitted for severe sepsis due to Salmonella infection. Before this admission, she had had no known neurologic abnormalities. A normal ophthalmologic examination with a pediatric ophthalmologist had occurred 1 month before admission. She required intubation, pressor support, and chest compressions for episodes of cardiac arrest. After extubation, she exhibited lingering reduced consciousness, left gaze deviation, and right hemiparesis. She failed to respond to verbal stimuli. A right extensor plantar reflex was present. Her eyes were fully deviated to the left and did not cross the midline to command, visual stimuli, or the oculocephalic maneuver. Both corneas were cloudy. Results of dilated fundus examination were unremarkable.

Brain MRI obtained during this episode showed diffuse parenchymal volume loss but was otherwise unremarkable. MRI spectroscopy was not performed. Electroencephalography showed diffuse slowing but no epileptiform activity. The hemiparesis, gaze deviation, and corneal edema had resolved within 1 week. The patient was discharged in her baseline state.

Stroke-like manifestations are well documented in many mitochondrial disorders, most notably the condition called mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) (8), but not in Pearson syndrome.

Reversible corneal edema has not been described in any mitochondrial disorder. We presume that in our patient this ocular manifestation, together with transient cerebral hemispheric dysfunction, were related to an exacerbation of impaired mitochondrial function triggered by the sepsis (9). Lee et al (3) described a 3-year-old girl with Pearson syndrome who was discovered to have persistent corneal haze and early retinitis pigmentosa in conjunction with acute pancreatitis. She died 4 months later without autopsy. Chang et al (5) reported the histopathologic results on the post-mortem cornea of a patient with KSS who died at age 27 and had had persistent corneal edema since age 4. It showed edema of the epithelium with areas of ballow separation, thickening of Descemet's membrane, and absence of the endothelium and Bowman's membrane. Boonstra et al (6) reported stromal and epithelial corneal edema by biomicroscopy as the initial sign of KSS in a 6-year-old boy. At age 14, biomicroscopic examination showed endothelial edema as well. Nakagawa et al (10) described improvement of corneal edema in an 11-year-old boy with KSS during treatment with antioxidants.

Brain MRI performed during stroke-like episodes in MELAS typically shows transient restricted diffusion predominantly affecting gray matter (11), a feature not seen in our patient. It is possible that a later MRI would have shown abnormalities. Magnetic resonance spectroscopy or positron emission tomography, reported to show abnormalities in mitochondrial disorders in which MRI appears normal might also have marked the left hemisphere dysfunction (12,13).

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Another Case of Leber Hereditary Optic Neuropathy in an Octogenarian

We read with interest the articles by Dagi et al (1) and Yu-Wai-Man et al (2) in this journal, which described 81- and 75-year-old patients with clinical findings and genetic testing consistent with Leber hereditary optic neuropathy (LHON). We recently examined a patient who developed slowly progressive painless vision loss in the right eye at age 81 years. He noted that the right eye stabilized after 3
months. Five months later, he developed a similar decline of vision in the left eye.

He had hypertension, prostate cancer, hypercholesterolemia, depression, and essential tremor. A deceased maternal cousin "went blind" at about the age of 60 of unknown cause. The patient had stopped smoking cigarettes 46 years earlier and drank alcohol occasionally.

Our examination disclosed best-corrected visual acuities of finger counting in both eyes. (Baseline visual acuities had been 20/25 in both eyes.) Both pupils constricted sluggishly and there was a 1+ afferent pupillary defect in the right eye. Fundus examination revealed pallor of the right optic disc and mild pallor of the left optic disc.

The patient denied symptoms of giant cell arteritis. Brain MRI and erythrocyte sedimentation rate, C-reactive protein, angiotensin-converting enzyme, syphilis, neuro-myelitis optica IgG serology, and vitamin B₁₂ test results were all normal. Genetic testing for LHON revealed the 11778 mutation.

The present case adds to the growing number of patients with LHON of clinical onset at an advanced age (1-3). In the proper clinical context, LHON testing even among octogenarians is a reasonable consideration for diagnosis and genetic counseling.

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Anterior Ischemic Optic Neuropathy After Intravitreal Injection of Bevacizumab

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) agent widely used for intravitreal treatment of neovascular and exudative ocular diseases, is generally free of complications, but lens injury, endophthalmitis, retinal detachment, subconjunctival hemorrhage, cataract progression, acute vision loss, central retinal artery occlusion, new or progressive subretinal hemorrhages, and tears of the retinal pigment epithelium have been reported (1). We describe a case of nonarteritic ischemic optic neuropathy (NAION) after intravitreal injection of bevacizumab, a complication not heretofore reported.

A 72-year-old woman presented with vision loss in her right eye from exudative age-related macular degeneration (ARMD). She had had an episode of NAION 10 years earlier in the right eye. Best-corrected visual acuity was light perception in the right eye and finger counting at 1 m in the left eye. An afferent pupillary defect was present in the right eye. Intraocular pressures were 12 mmHg in both eyes. Slit-lamp examination was unremarkable except for a nuclear cataract in both eyes. Fundus examination and retinal fluorescein angiography revealed optic disc pallor and dry ARMD in right eye and an active subfoveal choroidal neovascularization in left eye (Fig. 1).

The left eye underwent an intravitreal injection of 2.5 mg/0.1 mL bevacizumab. Four weeks later, visual acuity was light perception in the right eye and finger counting at 2 m in the left eye with decreased activity of the neovascular complex. Two weeks later, she underwent an additional intravitreal injection of 2.5 mg/0.1 mL bevacizumab. One week after the injection, she reported visual loss in the left eye on awakening.

On our examination, visual acuity was light perception in both eyes. Intraocular pressure was normal. Pupils were sluggishly reactive without afferent defect. The left optic nerve was now edematous with peripapillary hemorrhages (Fig. 2). She reported no symptoms of giant cell arteritis. Results of laboratory tests, including complete blood count, erythrocyte sedimentation rate, and serum C-reactive protein, were within the normal range.

Risk factors of NAION include crowding of the optic disc, systemic hypertension, diabetes, smoking, hyperlipidemia, and surgery (2). We propose the following possible mechanisms for NAION in our patient:

1. Impaired autoregulatory and microcirculatory mechanisms of optic nerve circulation due to pan-VEGF blockade. The exact mechanism responsible for blood flow autoregulation in the optic nerve remains enigmatic (3). Recent studies have shown that vascular endothelial vasoactive agents play an important role in modulating the local vascular tone and perhaps in blood flow autoregulation (3). Impaired autoregulation of the optic disc circulation by atherosclerosis, with a possible contribution from serotonin and endothelin-mediated vasospasm, may play a role in the pathogenesis of idiopathic NAION (4). Inhibition of VEGF may influence this autoregulation in the microcirculation. In addition, a sudden drop in effective VEGF concentration may be responsible for closure of normal capillaries (5).
2. Transient intraocular pressure (IOP) elevation after intravitreal injection of bevacizumab. A transient increase in IOP can lead to ischemia of the optic nerve head because of a decrease in perfusion pressure (6). Elevations in IOP immediately after intravitreal injections are common (7). However, this mechanism seems less likely because NAION occurred 7 days after the injection.

3. The NAION is an incidental occurrence. The risk of fellow eye involvement in NAION is 15-24% within 5 years (8). Because our patient had an attack of NAION in right eye, she was susceptible to this event in the fellow eye.

Given the widespread use of intravitreal anti-VEGF agents, a possible effect of VEGF blockade on optic nerve circulation merits further exploration.

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New International Classification of Diseases (ICD-11) Needs NANOS Input

We wish to invite NANOS members to contact us with their ideas about the upcoming revision of the International Classification of Diseases (ICD) (ICD-11), a project of the World Health Organization (WHO).

The International Council of Ophthalmology (ICO) has formed a Task Force to work with the WHO in this revision. The ICO Task Force for ICD-11, approved to form the Topic Advisory Group (TAG) for Eye Diseases by the WHO on December 9, 2008, is presently forming work groups that will serve as the key functioning units for the review of evidence and generation of proposals. To head the work group in neuro-ophthalmology the cochairs are John Keltner, MD (Sacramento, CA) and Satoshi Kashii, MD, PhD (Osaka, Japan).

The plans for ICD-11 are more extensive than those for previous revisions. The WHO intends to create a permanent Internet process involving a knowledge management and sharing portal similar to that used by the Internet encyclopedia Wikipedia. The new classification is to take advantage of modern data-processing capabilities and meet additional needs, such as those for electronic medical records. Previous classifications have not officially adopted a definition of disease. Linking ICD with standard terminologies such as the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) is one of the main aims of the revision process. We encourage readers to send comments or suggestions to us.

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**Principles and Practices of Ophthalmology, 3rd Edition**


Scope: This is the 3rd edition of a multiauthored, 4-volume text of modern ophthalmology. Its 5,461 pages include 417 chapters in 21 sections. There are two associate editors, 32 section editors, and 691 authors. It is heavily illustrated with pictures, most of which are in color. Each volume has its own index and the last volume has an index covering all 4 volumes, although misleadingly titled as the index for Volume 4.

Chapters include bulleted “key features” and tables. Basic science is no longer given its own volume, although much of it still appears in the sections on optics and low vision. Refractive surgery now warrants its own section, and there is a new section on ethics and professionalism.

Strengths: This edition differs from earlier editions in broadening the scope of authorship beyond Harvard. The inclusion of material on ethics and professionalism and the use of bulleted key features, tables, and color-coded tabs are helpful in passing on the take-home messages in an overwhelmingly extensive text.

Weaknesses: In a text of this immensity, there are bound to be errors of omission, commission, and redundancy. Topics are often needlessly repeated across chapters. Rare disease processes often receive a lot of attention, and common diseases often receive insufficient coverage.

Recommended Audience: This latest edition remains a valuable source for medical students, residents, practitioners, and educators.

Critical Appraisal: If current trainees in medicine are going directly to online sources for their education, they are missing out on a valuable resource such as this. Experts have filtered the material and provided eminence-based choices together with evidence-based choices. Although texts like this cannot be rapidly updated, they offer—in one place—a carefully crafted and seasoned point of view.

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**Advances in Understanding Mechanisms and Treatment of Infantile Forms of Nystagmus**


Scope: This is a 240-page hardcover book covering the diagnosis, management, and research in nystagmus of infancy and childhood. A compendium of a 2-day conference dedicated to the life-long efforts of Louis F. Dell’Osso, PhD, it contains contributions from international experts. The first section deals with psychophysical aspects of infantile nystagmus and the relative contributions of extraocular proprioception and efference (corollary) discharge. The second section reviews animal and development models of strabismus, amblyopia, and nystagmus. The third section presents basic genetic studies and clinical trials of drug and surgical treatment of infantile nystagmus. The fourth section pulls together a range of contributions dealing with normal gaze control, infantile nystagmus, and acquired disorders of eye movements, including new treatment measures.

Strengths: This textbook is clearly and accurately written in a simple and easily understood style. There are ample tables, illustrations, and references to supplement the text. The translational nature of the research and the multidisciplinary contributions to this field are clearly evident in the chapter subjects and diverse authorship. The descriptions of modern electrophysiologic evaluation and investigation of the ocular motor system and its diseases are embedded in most chapters.

Weaknesses: The content is probably not deep enough in any one area to completely satisfy the clinician or the scientist involved with the care or research of this patient population.

Recommended Audience: This textbook should appeal to those in a variety of disciplines, including neurology, ophthalmology, optometry, engineering, developmental physiology, psychology, and psychiatry.

Critical Appraisal: Dedicated to the career of an outstanding researcher who has served as a mentor to many people and redirected an entire discipline, this book covers a narrow field but should be of interest to a wide audience.
It will be a valuable resource for scientists and practitioners interested in developmental disorders of vision.

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Clinical Ocular Toxicology: Drugs, Chemicals, and Herbs

Frederick T. Fraunfelder, MD, Frederick W. Fraunfelder, MD, and Wiley A. Chambers, MD.
ISBN 978-1-4160-4673-8, $149.00.

Scope: This text serves as a clinical guide for clinicians to diagnose and manage ocular problems related to interactions with drugs, chemicals, and herbal supplements. It includes an introduction on ocular toxicology and important clinical information on several classes of medications. It also includes illustrations of selected ocular toxicities.

Parts 1 through 6 provide background on ocular pharmacology. Part 1 (Principles of Therapy) reviews pharmacodynamics, pharmacokinetics, and pharmacologic principles. Part 2 (Ocular Drug Delivery and Toxicology) reviews basic pharmacology and toxicity of topical medications, including preservatives, vehicles for topical medication delivery, toxic responses, and application of topical ocular medication. Part 3 (Methods for Evaluating Drug-Induced Visual Side Effects) reviews testing and other considerations when evaluating for possible drug toxicity. Part 4 (The Role of Electrophysiology and Psychophysics in Ocular Toxicology) reviews the role of electrophysiology in drug testing and drug development. Part 5 (National Registry of Drug-Induced Ocular Side Effects) reviews the rationale for a national drug registry and provides steps for reporting cases. Part 6 (Herbal Medicines and Dietary Supplements) reviews the current use of dietary supplements to treat eye disease. Parts 7–9 summarize the ocular side effects of drugs, chemicals, and herbal medicines. Part 10 includes a list of suspected drugs for each possible ocular side effect. Part 11 is the subject index for the book.

Strengths: There are several improvements to this book compared with its predecessor, Drug-Induced Ocular Side Effects. It includes a review of 70 new drugs, has valuable illustrations, and covers ocular side-effects related to chemicals and herbal remedies. The section on chemicals is particularly well organized and concise. It provides an extremely valuable resource to ophthalmologists fielding questions from emergency departments about ocular chemical exposures. One of the best features of this book is the aggregating of ocular side-effects by likelihood of causality (certain, probable, possible, or conditional/unclassified). The color-coded index of side effects at the end of the book effectively summarizes a great deal of data in an easily accessible format.

The authors also include useful recommendations on how to manage patients experiencing pharmacologic side effects.

Weaknesses: The quantification of probability of causality is often based on the impression of the authors rather than on scientific evidence. There are scant comments on medication dosage. For instance, cimetidine is mentioned as a treatment for conjunctival papillomas. However, no indication of an appropriate dosage is mentioned. This information may be outside of the scope of the current edition, but I would encourage the authors to consider providing dosing information, particularly for medications such as cimetidine, which are rarely used by ophthalmologists. Some of the illustrative photographs are not of high quality. Drug names are not differentiated by color or font, making identification sometimes a slow-going process.

Recommended Audience: This text serves as a concise and reliable guide for practitioners. The new features have broadened its audience. The photos and introductory sections serve as a powerful tool for those starting to study the field.

Critical Appraisal: This book serves as the definitive guide for ocular toxicity for the clinician. Considering that one author is the founder and director of the National Registry of Drug-Induced Ocular Side Effects, it is authoritative. Pick up a copy for your office.

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The Ocular Fundus: From Findings to Diagnosis

Sebastian Wolf, MD, Bernd Kirchhof, MD, and Martin Reim, MD.
ISBN 3-13-139371-8, $149.95.

Scope: This 236-page hardcover volume is basically a portrait gallery of ocular fundus conditions. The work
of three eminent German retina specialists, it grew out of their sense that examiners were uncertain about what they were seeing and had a “tendency to fall back on relatively few diagnoses.”

The text is built around 309 illustrations, mostly superb fundus photographs. It seems to be organized according to the pathologic unit—abnormal retinal vessels, bleeding, tumors, vitreous opacities—but the reader is likely to miss the organization and concentrate on the pictures. Text and tables go with the pictures, but they are mostly trimming.

Strengths: The photos are beautiful. There are iconic representations from every important pathologic process in the fundus.

Weaknesses: The text provides only rudimentary information. It cannot stand alone.

Recommended Audience: If the authors are correct that even well-trained ophthalmologists would not be familiar with the classic fundus findings of the major conditions, then practitioners will find this book helpful. Medical students will certainly love it, as will nonophthalmic physicians and ophthalmic technicians and nurses.

Critical Appraisal: This is a “best-in-show” of fundus abnormalities. Although such material is now available free online, this book is a higher quality product. Libraries in teaching institutions will undoubtedly want to purchase it.

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The emphasis is on neuroanatomy. There is also a section on neurologic indications for cranial MRI, including vascular tumor, infection, inflammation, trauma, hydrocephalus, and congenital malformations.

Strengths: As the new generation of students becomes increasingly dependent on the Web and electronic sources, this CD attempts to bridge the gap between traditional texts and a more interactive mode of learning.

Weaknesses: There are several mistakes. Particularly frustrating to a neuro-ophthalmologist is the labeling of the occipital lobe on CT as the cerebellum, labeling the internal carotid artery on MRI as the trigeminal nerve, and identifying the facial nerve as the trigeminal nerve. Missing from the orbit is the superior oblique muscle, and the posterior ethmoid sinus is labeled as the nasal cavity. There is also lack of detail about the sphenopalatine and pterygomaxillary areas. In addition, the cavernous sinus is not identified, and there is no identification of the inferior orbital fissure or the cranial nerves below it. In some instances, there are multiple examples when one would do.

Recommended Audience: Neurologists just beginning to learn about neuro-imaging are most apt to find this CD useful.

Critical Appraisal: The convenience and the immediate feedback of an interactive CD has advantages. Missing is a proper attention to detail.

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NeuroImaging in Neurology: An Interactive CD

David C. Preston, MD, and Brenda E. Shapiro, MD, PhD.

Scope: This CD is an interactive collection of 2,100 images from patients. It is designed as an introduction to neuro-imaging in neurology. Running on a PC or Mac, it is divided into sections covering normal imaging with magnetic resonance of the brain and spine, plus short sections on MRA, magnetic resonance venography, CT of the brain, and conventional angiography. It has several brief PowerPoint presentations on basic analysis aimed at the novice.

Greenfield’s Neuropathology, 8th Edition

Seth Love, PhD, FRCP, FRCPath, David N. Louis, MD, and David W. Ellison, MD, PhD, FRCPath.

Scope: This is an excellent new edition of this classic known in the neuropathology community as “The Bible.” As stated by the authors in the Preface, “the emphasis in much of the present book is on an integrated approach to diagnosis taking account of the clinical manifestations, neuroradiologic and laboratory findings, as well as the neuropathological and molecular genetic features of the different diseases.”
The 2-volume book is divided into 24 chapters covering a comprehensive range of pathologic entities including pathologic reactions in the central nervous system, pediatrics, vascular diseases, trauma, infectious diseases, multiple sclerosis and other demyelinating diseases, nutritional and metabolic disorders, aging, dementia and other neurodegenerative diseases, psychiatric diseases, epilepsy, peripheral nerve and muscle, and tumors. There is a strong emphasis on molecular mechanisms, as well as clinical and laboratory correlation.

Strengths: The eighth edition benefits from extensive reorganization and the addition of outstanding new contributors. The chapters now emphasize a more “practical” approach to the material aided by the addition of many diagrams, text boxes, and tables. This edition includes a CD-ROM containing more than 2,700 images of the figures and diagrams in the book. The images can be easily downloaded as JPG files or transferred to PowerPoint for presentation purposes, an extraordinary benefit for teachers.

Weaknesses: It is difficult to find any weakness in the book. I personally miss the initial introductory chapters of past editions, which contained more basic neurobiology of the neuron and glia. The absence of a chapter on ophthalmic pathology is greatly missed especially in view of the increasing role of neuropathologists in diagnosing ophthalmic specimens and educating neuropathology trainees.

Recommended Audience: The book is an outstanding resource for basic and clinical neuroscientists, neuropathologists, neurologists, neurosurgeons, and neuroophthalmologists.

Critical Appraisal: The eighth edition certainly carries on Greenfield’s tradition of being the ultimate reference text in neuropathology.

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The essays were entitled The History of Disease (Kiple), The Rise of Medicine (Nutton), What Is Disease ? (Porter), Primary Care (Shorter), Medical Science (Porter), Hospitals and Surgery (Porter), Drug Treatment and the Rise of Pharmacology (Weatherall), Medicine, Society and the State (Pickstone), and Looking to the Future—1996 (Watts).

Cambridge University Press has now published the essays without illustrations in a softcover edition of about 400 pages.

Strengths: Many of the useful appendices of the 1996 book have been retained in this 2006 version, including a thorough general index, a fascinating 14-page chronology of medical events throughout history, a table of 50 major human diseases, their cause and the means of their transmission; four tightly printed pages of notes from the various essays; a list of 225 titles suggested for further reading, arranged by chapter, and an index of the major medical personalities mentioned.

Roy Porter, the editor, was a professor in the Cambridge University history department who spent several years at the Wellcome Institute for the History of Medicine. Porter himself wrote 38% of the text of this book. He died in 2002. Of Porter, Nicholas Lezard said in a book review: “He has written about a dozen books in roughly as many years. They are all ferociously learned yet utterly readable, and he hardly ever repeats himself as far as I can see. How the hell does he do it?’’

Weaknesses: None.

Recommended Audience: This book is recommended to anyone with an interest in the history of medicine.

Critical Appraisal: This book is not expensive, and a few hours spent dipping into it will be rewarding. The history of our profession is inevitably part of our personal history. Each of us should know something about where our profession has been and what it has done, because that history has influenced who we are today.

H. Stanley Thompson, MD
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The book is divided into 9 chapters. The first chapter defines the study of neuroethics and its utility, illustrating its application to various test cases such as prosopagnosia and neglect. Here the author also introduces the "extended mind" hypothesis, the idea that human minds extend beyond the skull to include external resources used in thinking, such as pens and paper, to which he returns throughout the book. The second chapter explores direct and indirect manipulations of the mind via traditional and new methods, examining arguments regarding their impact on self-identity. Chapters 3 and 4 further explore moral arguments for and against direct manipulations of the mind, contrasting them with often overlooked indirect manipulations via the external environment. Chapter 5 is an in-depth discussion of neuroethics and memory, concluding that potential alterations to memory brought about by neuroscientific advances are not ethically unique from dilemmas of memory alteration in existence. Chapters 6 and 7 tackle the neuroscientific and neuroethical debate surrounding the concepts of self and free will. The author suggests a biologic basis for viewing self-control as a limited resource, an idea known as ego-depletion. Chapter 8 explores the idea of self-deception and its origins using anosognosia and blindsight as examples. The final chapter discusses the neuroscience of ethics itself, in particular the physiologic underpinnings of human intuition and its role in morality.

Strengths: This is a wide-ranging, well-written, intellectually engaging monograph that successfully convinces the reader of the need for neuroethics discourse by individuals involved in basic, cognitive, and clinical neurosciences. It is an important contribution to the growing literature in this up-and-coming field. The author is well-versed in philosophy, psychology, and neuroscience and blends his impressive knowledge base to explore current debate and defend several fascinating hypotheses.

Weaknesses: A reader unaccustomed to philosophic debate may get lost as the author tackles complex phenomena from the perspectives of philosophy, neuroscience, moral psychology, and ethics. Ambitious in its scope, the text may be of limited interest to those looking for specific application to neuro-ophthalmology.

Recommended Audience: This book is layered in its complexity and has something to offer readers at all levels of familiarity with the topic. Any reader with a strong interest in the philosophical and ethical implications of the neurosciences will want to read it. However, the book was written primarily at a graduate student level, limiting its potential audience.

Critical Appraisal: The author has produced a seminal work in a field that is emerging from infancy. This book is an invaluable resource for those with an interest in the intersection of basic and clinical neuroscience, philosophy, and ethics. To this end, the author has done a fine job peering into the human mind and exploring current and upcoming ethical and philosophical conundrums. It is a fascinating and challenging read.

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Upcoming Meetings

June 13–June 16, 2009
17th Congress of the European Society of Ophthalmology
Amsterdam, The Netherlands
http://www.soe2009.org/
Contact: soe2009@congrex.com

June 17–June 20, 2009
9th European Neuro-Ophthalmology Society Meeting
Lubeck, Germany
http://www.euros2009.org/
Contact: detlef.koempf@neuro.uni-luebeck.de

June 20–June 24, 2009
19th Meeting of the European Neurological Society
Milan, Italy
http://www.akm.ch/ens2009/
Contact: info@ensinfo.org

June 20–June 23, 2009
Canadian Ophthalmological Society Annual Meeting
Toronto, ON
http://www.eyesite.ca/english/amindex.htm
Contact: cos@eyesite.ca

Sept. 10–Sept. 13, 2009
14th International Headache Congress/51st Annual Scientific Meeting
Philadelphia, PA
http://www.ihc2009.org/
Contact: ihc2009@talley.com

Sept. 12–Sept. 15, 2009
13th Congress of the European Federation of Neurological Societies (EFNS)
Florence, Italy
http://efns2009.efns.org/
Contact: efns09@kenes.com

Sept. 16–Sept. 18, 2009
32nd Annual Meeting of the Japan Neuroscience Society
Nagoya, Japan
Contact: neuroscience2009@jnss.org

Sept. 25–Sept. 26, 2009
Practical Pearls in Neuro-Ophthalmology
Toronto, ON
http://events.cmetermino.ca/website/index/opt0907
Contact: help-OPT0907@cmetermino.ca

Sept. 30–Oct. 3, 2009
European Association for Vision and Eye Research (EVER) Annual Congress
Portorož, Slovenia
http://www.ever.be
Contact: ever@ever.be

134th Annual Meeting of the American Neurological Association
Baltimore, MD
http://www.anetical.org
Contact: anameeting@llmsi.com

Oct. 17–Oct. 21, 2009
39th Annual Meeting of the Society for Neuroscience
Chicago, IL
http://www.sfn.org/am2009/
Contact: info@sfn.org

Joint Meeting of the 29th Pan-American Congress of Ophthalmology
113th Annual Meeting of the American Academy of Ophthalmology
San Francisco CA
http://www.aao.org/meetings/annual_meeting/sanfrancisco.cfm
Contact: meetings@aao.org

59th Annual Meeting of the Congress of Neurological Surgeons
New Orleans, LA
http://www.neurosurgeon.org/meetings
Contact: info@1cns.org

19th World Congress of Neurology
Bangkok, Thailand
http://www.wcn2009bangkok.com/
Contact: wcn2009@congrex.com

American Society of Neuroimaging 2010 Annual Meeting
San Francisco, CA
http://www.asnweb.org
Contact: asn@llmsi.com

Feb. 24–Feb. 26, 2010
International Stroke Conference
San Antonio, TX
http://strokeconference.americanheart.org/
Contact: strokeconference@heart.org
March 6–March 12, 2010
Tucson, AZ
http://www.nanosweb.org/meetings/nanos2009/
Contact: info@nanosweb.org

March 23–March 26, 2010
19th International Visual Field and Imaging Symposium
Tenerife, Spain
http://www.ips2010.es/
Contact: ips2010@ips2010.es

May 2–May 6, 2010
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Ft. Lauderdale, FL
http://www.arvo.org
Contact: arvo@arvo.org

June 5–June 9, 2010
World Ophthalmology Congress
XXXII International Congress of Ophthalmology (ICO)
108th DOG Congress (German Society of Ophthalmology)
AAD Congress 2010 (German Academy of Ophthalmology)
Berlin, Germany
http://www.woc2010.de/

June 15–June 18, 2010
XVIII International Neuro-Ophthalmology Society Meeting
Lyon, France
http://www.inos2010.org
Contact: inos2010@carco.fr

July 3–July 7, 2010
Forum of European Neuroscience Societies (6th)
Amsterdam, The Netherlands
http://fens2010.neurosciences.asso.fr/
Contact: E-mail form on above Web site

July 14–July 19, 2010
8th IBRO World Congress of Neuroscience
Florence, Italy
http://www.ibro2011.org/site/home.asp
Contact: ibro2011@newtours.it

July 17–July 22, 2010
XII International Congress on Neuromuscular Diseases
Naples, Italy
http://www.icnmd2010naples.org/
Contact: ICNMD2010@congrex.com

July 18–July 23, 2010
XIX Biennial Meeting of the International Society for Eye Research
International Congress on Eye Research (ICER)
Montreal, QC
http://www2.kenes.com/iser2010/pages/home.aspx
Contact: mail@iser.org

Sept. 11–Sept. 15, 2010
XVIIth International Congress of Neuropathology
Salzburg, Austria
http://www.icn2010.org/
Contact: Brigitte.millan-ruiz@meduniwien.ac.at

7th World Stroke Congress
Seoul, Korea
Contact: stroke2010@kenes.com