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Uncommon Presentations of Uncommon Conditions

Amy Pruitt, MD

Neuro-ophthalmologists evaluate patients who often baffle other physicians due to unusual presentations of uncommon conditions. Vigilance and suspicion of even minor atypical clinical findings or subtle imaging abnormalities are desirable professional traits. Three articles (1–3) in this issue of the Journal illustrate such uncommon dilemmas and provide instructive caveats.

Zunz et al (1) present a pediatric case of gliomatosis cerebri (GC) initially diagnosed as idiopathic intracranial hypertension (IIH). The child’s age was in the demographic in which approximately 50% of IIH patients are male and also in the appropriate demographic for pediatric GC. No seizures or focal deficits hinted at a more typical presentation of GC. We are not told the patient’s body mass index, although fewer children with IIH are obese when compared to the adult population. At initial presentation, the results of patient evaluation met the criteria for IIH with bilateral papilledema, a sixth nerve palsy, and normal lumbar puncture results save for elevated opening pressure. Mindful that secondary causes of IIH are more common in pediatric than adult patients (4), the authors attempted to exclude the most treatable mimics of IIH, including cerebral venous sinus thrombosis and infiltrating neoplasm. Initial neuroimaging with CT and CT venography was unremarkable. One month later, when MRI and magnetic resonance venogram (MRV) were performed, only subtle imaging clues pointed to a diagnosis other than IIH.

Histologic diagnosis of GC is essential as new techniques offer additional information of prognostic and possibly therapeutic significance. Mitotic index was high in this patient, signifying aggressive tumor behavior. Although not discussed in the report by Zunz et al (1), the presence of mixed oligodendrocytes may confer a better prognosis, particularly when the genetic alteration 1p/19q codeletion is present. For such patients, initial use of temozolomide chemotherapy may be an option and whole brain radiation can then be deferred until later in the clinical course. Recently, isocitrate dehydrogenase 1 and 2 (IDH 1 and IDH 2) mutations were identified in adult glioblastomas with better prognosis (5). The mutations are not seen in primary glioblastoma but occur in 75% of other adult diffuse astrocytic and oligodendrogial tumors (6). The IDH 1 genetic alteration, seen only in adult patients in a study of GC that included 3 pediatric GC cases, conferred a trend toward longer overall survival (10.5 months in nonmutated vs 43.5 months in mutated GC) (7). GC usually behaves aggressively even when histologic features of high-grade astrocytic tumor are absent. The prognosis among children is 64% with 2-year overall survival (8), approximately the same as adults (9). The impact of adjuvant temozolomide for GC appears to improve survival in some early small studies (10).

Noval et al (2) describe neuro-ophthalmic findings in 24 cases of primary diffuse leptomeningeal gliomatosis (PDLG) without brain parenchymal disease. PDLG has a short aggressive course but initially may cause only nonlocalizing signs and symptoms including headache, altered mental status, papilledema, and sixth nerve palsies. MRI shows nodular meningeal enhancement and communicating hydrocephalus mimicking chronic infectious meningitis with hypoglycorrachia. If spinal fluid cultures are uninformative, meningeal biopsy may be necessary. The 2 index cases reported by Noval et al (2) make a plausible case for tuberculosis (TB) meningitis, and with institution of steroids along with anti-TB medications, there was transient clinical improvement. However, the patients survived only 5–22 months. Of the 24 cases reviewed, the 3 patients who survived more than 1 year all received corticosteroids, temozolomide, and radiation therapy.

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Occasionally, patients with leptomeningeal gliomatosis develop GC (11). This may become more frequent with the new recurrence pattern of brain tumors in patients treated with antiangiogenic agents, such as bevacizumab. Preclinical studies suggest that antiangiogenic therapies promote glioma invasiveness and up to 30% of recurrences may be nonenhancing multilobar infiltrative tumor similar to GC or leptomeningeal dissemination. The combination of headache, sixth nerve palsies, and visual loss in these patients undoubtedly will prompt many referrals for neuro-ophthalmic evaluation (12).

Sudhakar et al (3) confront the great neuro-oncologic mimicker, primary central nervous system lymphoma (PCNSL), and use diffusion-weighted imaging (DWI) to assist in the diagnosis of lymphomatous infiltration of the optic nerve. Their patient developed sudden painful complete loss of vision in the right eye 4 months following the diagnosis of non-Hodgkin B-cell Burkitt-type lymphoma and after 4 cycles of chemotherapy. DWI with apparent diffusion coefficient (ADC) maps was consistent with restricted diffusion. Cerebrospinal fluid (CSF) flow cytometry and cytomorphology were positive for a B-cell neoplasm. While cytologic examination of the CSF was normal 4 months after intrathecal and systemic chemotherapy, vision remained poor, and MRI showed decreased enhancement. DWI with apparent diffusion in lymphomatous optic neuropathy. J Neuroophthalmol. 2011;31:306–309.

REFERENCES
Neuro-Ophthalmological Features of Primary Diffuse Leptomeningeal Gliomatosis

Susana Noval, MD, PhD, Santiago Ortiz-Pérez, MD, Bernardo F. Sánchez-Dalmau, MD, Gerardo Ruiz-Ares, MD, Javier Arpa, MD, PhD, Alfredo Adán, MD, PhD

Abstract: We performed an in-depth study of the neuro-ophthalmologic signs and symptoms of a rare but fatal disease known as primary diffuse leptomeningeal gliomatosis (PDLG). Two new cases of PDLG are described, and 22 published cases reviewed. Papilledema and sixth nerve palsy are the most common neuro-ophthalmic findings. Other abnormalities include third and fourth nerve palsies, nystagmus, and vision loss. Involvement of the visual system may be part of the initial presentation of PDLG.

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Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare and fatal disease characterized by diffuse infiltration of the meninges by neoplastic glial cells without evidence of tumor within the parenchyma of the brain or spinal cord. These neoplastic cells are thought to arise from heterotopic glial nests in the leptomeninges (1,2). Cooper and Kernohan (3) proposed the following diagnostic criteria: no apparent attachment of extramedullary meningeal tumor to the neural parenchyma, no evidence of primary neoplasia within the neuraxis, and the existence of distinct leptomeningeal encapsulation around the tumor. The mean age of clinical onset is 34 years, but it may appear at any age, ranging from 1 to 80 years (1,2,4). PDLG shows male predominance (5). The most striking features include rapid onset, short prodromal phase, and an aggressive course.

Clinical presentation includes a variety of neurological symptoms, including headache, cranial nerve involvement, vomiting, meningismus, and decreased mental status (4). Raised intracranial pressure is the most constant sign as a result of communicating hydrocephalus, with papilledema and sixth nerve palsy as the most frequent neuro-ophthalmic signs reported (1,6). Visual symptoms are often vague at initial clinical presentation (7), and blindness usually develops late in the course of the disease (1,8,9).

Diagnosis of PDLG is often challenging because the clinical picture is similar to chronic infectious meningitis or polyradiculopathy, and cerebrospinal fluid (CSF) analysis is frequently nonspecific (5,10). Tuberculous meningitis is often suspected as the initial diagnosis, and patients may be started on antituberculosis therapy (1).

We describe 2 patients with PDLG who presented with prominent visual symptoms. Their clinical course is added to the clinical profile of other cases of PDLG.

CASE REPORTS

Case 1
A 19-year-old woman was seen in consultation for headaches and behavioral changes. Six days later, she complained of a sudden reduction of vision in the right eye. Bilateral sixth nerve palsies and neck stiffness developed rapidly. On examination, visual acuity was light perception, right eye, and 20/20, left eye, and bilateral papilledema was noted. Brain MRI and MRA were unremarkable. Lumbar puncture demonstrated an elevated opening pressure of 50 cm H₂O with low glucose of 29 mg/dL (normal: 55–75 mg/dL), increased protein of 49 mg/dL (normal: 15–45 mg/dL), and 10 white blood cells per cubic millimeter.

Treatment for presumed tuberculous meningitis was started withisoniazid, rifampicin, ethambutol, pyrazinamide, and prednisone. However, visual acuity fell to light perception in both the eyes, with pupils reacting poorly
to light. Within one month, diffuse optic atrophy was present bilaterally.

Blood tests, immunologic studies, and tumoral markers were normal. Repeat lumbar puncture revealed CSF adenosine deaminase activity of 21.9 U/L (>20 U/L supportive of the diagnosis of tuberculous meningitis). CSF cultures and serologies were negative, and cytology did not show the presence of malignant cells. Brain and meningeal biopsies were nondiagnostic. Six weeks after the onset of symptoms, MRI revealed widespread meningeal thickening of the brain and the spinal cord and enhancing nodular lesions (Fig. 1).

The patient continued to deteriorate clinically developing respiratory insufficiency and tetraparesis. She died 22 weeks after the presentation. Postmortem examination revealed diffuse, whitish, granular thickening of the meninges. The subarachnoid space was infiltrated with glial cells, which had numerous Rosenthal fibers and expressed glial fibrillary acidic protein and the p53 gene (Fig. 2A). The glial cells surrounded and compressed the vasculature, some cranial nerves, and the pineal gland. The lower brainstem showed extensive hemorrhagic necrosis. No evidence of a primary tumor was found in the brain or spinal cord parenchyma.

**Case 2**

A 17-year-old woman presented with generalized weakness, vomiting, and epigastric pain, and 4 days later, she developed diplopia. Examination documented vision of 20/20 in both eyes, with bilateral sixth nerve palsies and a partial right third nerve palsy. Three days later, she complained of visual impairment in the right eye and was found to have acuity of light perception, right eye and 20/20, left eye. A right relative afferent pupillary defect was detected, and the fundi were normal. Optic disc pallor developed in the right eye over the course of several weeks.

Brain MRI demonstrated diffuse leptomeningeal enhancement without evidence of intraparenchymal lesions (Fig. 3A). Analysis of CSF did not show malignant cells but increased protein of 77 mg/dL (normal: 15–48 mg/dL),

**FIG. 1.** Case 1. Contrast-enhanced T1 MRI showing meningeal thickening with enhancement (arrows) of the brain (A) and spinal cord (B, C).
pleocytosis (10 white blood cells/mm\(^3\)), and low glucose of 27 mg/dL (normal: 55–75 mg/dL) were detected. A diagnosis of probable tuberculous meningitis was made, and an empiric treatment with antituberculous medications and steroids was initiated.

The patient developed cognitive dysfunction, meningeal signs, and hydrocephalus that required placement of a ventriculoperitoneal shunt. Follow-up brain MRI showed additional lesions in the subarachnoid space including the skull base and the spinal cord (Fig. 3B). A brain biopsy was performed, which disclosed anaplastic glial cells within the leptomeninges consistent with PDLG (Fig. 2B, C). Treatment included radiotherapy (brain, spinal cord) and chemotherapy with temozolomide. No significant improvement was observed. The patient slowly deteriorated and died due to respiratory failure 15 months after initial presentation.

**DISCUSSION**

PDLG is a rare condition that produces a clinical picture similar to chronic infectious meningitis (9). Due to the variability of clinical presentation, clinical diagnosis is often challenging, and meningeal biopsy is required (1). Differential diagnosis includes infectious meningoencephalitis, meningeal carcinomatosis, secondary meningeal gliomatosis, and autoimmune and inflammatory diseases affecting the meninges (11,12).

Early in the course of the disease, MRI of the central nervous system may be normal. With progression of the disease, ventriculomegaly and diffuse or focal contrast-enhancing leptomeningeal thickening with no discernible intraaxial component are the most frequent neuroimaging findings. These leptomeningeal abnormalities may be restricted to the spinal cord or may be associated with contrast enhancement of the basal cisterns, cerebellum, brainstem, and cerebral hemispheres. Ischemic changes have also been
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<tr>
<th>Author, Year</th>
<th>Age, Years (Sex)</th>
<th>Visual Symptoms-Signs at Presentation</th>
<th>Later Visual Symptoms-Signs</th>
<th>Neurosurgery</th>
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<th>Survival (Months)</th>
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<tr>
<td>Sumi et al, 1968 (22)</td>
<td>61 (M)</td>
<td>III NP, amaurosis, pupillary areflexia</td>
<td>Sphenoid bone biopsy</td>
<td>—</td>
<td>Antibiotics</td>
<td>—</td>
<td>5</td>
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<td>Bhrany et al, 1974 (17)</td>
<td>46 (F)</td>
<td>Small pupils with sluggish reaction, left VI NP, papilledema</td>
<td>—</td>
<td>VPS, brain biopsy</td>
<td>—</td>
<td>—</td>
<td>22</td>
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<td>Bailey et al, 1985 (20)</td>
<td>53 (M)</td>
<td>Diplopia, left VI NP</td>
<td>Bilateral VI NP</td>
<td>VPS</td>
<td>Yes</td>
<td>Steroids, amphotericin, 5-fluorocytosine</td>
<td>3</td>
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<tr>
<td>Kitahara et al, 1985 (27)</td>
<td>15 (F)</td>
<td>Nystagmus on lateral gaze, upward gaze palsy, papilledema</td>
<td>—</td>
<td>VPS</td>
<td>—</td>
<td>Intrathecal ACNU, brain radiation</td>
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<td>Davila et al, 1993 (24)</td>
<td>38 (M)</td>
<td>Multidirectional nystagmus, left ophthalmoplegia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Intrathecal methotrexate, brain radiation</td>
<td>3</td>
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<tr>
<td>Giordana et al, 1995 (18)</td>
<td>49 (F)</td>
<td>Diplopia, papilledema, bilateral VI NP</td>
<td>—</td>
<td>VPS, SMB</td>
<td>—</td>
<td>Intrathecal methotrexate, AraC</td>
<td>4</td>
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<tr>
<td>Rogers et al, 1995 (28)</td>
<td>21 (M)</td>
<td>Papilledema, left VI NP</td>
<td>Optic disc pallor RE, papilledema LE, gaze-evoked nystagmus</td>
<td>VPS, BMB</td>
<td>—</td>
<td>Neuroaxis radiation</td>
<td>50</td>
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<td>Kobayashi et al, 1996 (29)</td>
<td>60 (M)</td>
<td>Blurred vision, papilledema with retinal hemorrhage</td>
<td>—</td>
<td>BMB</td>
<td>—</td>
<td>Spinal radiation, antineoplastic drugs</td>
<td>11</td>
</tr>
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<td>Olivera-Leal et al, 1997 (23)</td>
<td>24 (F)</td>
<td>Acute visual loss, pupillary areflexia, left medial rectus paresis</td>
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<td>—</td>
<td>—</td>
<td>Antibiotics, steroids</td>
<td>4</td>
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<td>Verslegers et al, 1998 (30)</td>
<td>7 (M)</td>
<td>Diplopia, anisocoria, right VI NP</td>
<td>BMB</td>
<td>—</td>
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<td>Paulino et al, 1999 (8)</td>
<td>9 (F)</td>
<td>Diplopia, strabismus and papilledema</td>
<td>Blindness</td>
<td>BMB</td>
<td>—</td>
<td>Steroids, etoposide, carboplatin, vincristine, intraventricular topotecan, craniospinal irradiation</td>
<td>Unknown</td>
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<tr>
<td>Trivedi et al, 2000 (14)</td>
<td>81 (M)</td>
<td>Vertical diplopia, left IV NP</td>
<td>—</td>
<td>Brain biopsy</td>
<td>—</td>
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<td>Corsten et al, 2001 (6)</td>
<td>44 (M)</td>
<td>—</td>
<td>Nystagmus on right lateral gaze</td>
<td>VPS, SMB</td>
<td>Yes</td>
<td>Steroids, neuroaxis irradiation</td>
<td>Unknown</td>
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<td>Rees et al, 2001 (9)</td>
<td>34 (F)</td>
<td>Papilledema, bilateral VI NP</td>
<td>Blindness</td>
<td>VPS, BMB</td>
<td>Yes</td>
<td>Steroids</td>
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</tr>
<tr>
<td>Author, Year</td>
<td>Age, Years (Sex)</td>
<td>Visual Symptoms-Signs at Presentation</td>
<td>Later Visual Symptoms-Signs</td>
<td>Neurosurgery</td>
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<td>Treatment</td>
<td>Survival (Months)</td>
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<tr>
<td>Baborie et al, 2001 (1)</td>
<td>71 (M)</td>
<td>Intermittent diplopia, no palsy or papilledema</td>
<td>Bilateral VI NP, papilledema with hemorrhages</td>
<td>—</td>
<td>Yes</td>
<td>Steroids</td>
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<td>Tsui et al, 2001 (25)</td>
<td>23 (F)</td>
<td>Blurred disc margin</td>
<td>Bilateral VI NP with normal ICP</td>
<td>—</td>
<td>Yes</td>
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<td>Bohner et al, 2005 (31)</td>
<td>25 (M)</td>
<td>Right VI NP</td>
<td>—</td>
<td>SMB</td>
<td>—</td>
<td>Vincristine, carboplatin</td>
<td>5</td>
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<td>Yomo et al, 2007 (5)</td>
<td>52 (M)</td>
<td>—</td>
<td>Bilateral VI NP, papilledema</td>
<td>VPS, BMB</td>
<td>—</td>
<td>Antibiotics, thiamine, neuroaxis radiation, ranimustine, interferon</td>
<td>3</td>
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<td>Watanabe et al, 2008 (12)</td>
<td>48 (F)</td>
<td>Diplopia, visual field defects, right VI NP, papilledema</td>
<td>—</td>
<td>BMB</td>
<td>—</td>
<td>Neuroaxis radiation, ACNU, interferon</td>
<td>11</td>
</tr>
<tr>
<td>Ko et al, 2009 (10)</td>
<td>24 (M)</td>
<td>Diplopia, blurred vision, acuity: HM in RE, 20/50 in LE, bilateral VI NP, papilledema</td>
<td>Elevated optic nerves nasally with temporal pallor</td>
<td>Ventriculostomy, BMB</td>
<td>—</td>
<td>Steroids, vancomycin, aztreonam, cyclophosphamide</td>
<td>6</td>
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<tr>
<td>Jicha et al, 2009 (4)</td>
<td>24 (M)</td>
<td>Intermittent horizontal diplopia, papilledema</td>
<td>—</td>
<td>BMB</td>
<td>—</td>
<td>Steroids, temozolomide, BCNU, radiotherapy</td>
<td>15</td>
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<td>Current study</td>
<td>19 (M)</td>
<td>Tunnel vision, papilledema</td>
<td>III NP with fixed pupil</td>
<td>BMB</td>
<td>—</td>
<td>Steroids, temozolomide, craniospinal radiation</td>
<td>13</td>
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<tr>
<td>19 (F)</td>
<td>Acute visual loss: light perception bilaterally, nonreactive pupils, bilateral VI NP, papilledema</td>
<td>—</td>
<td>VPS, BMB</td>
<td>Yes</td>
<td>Steroids</td>
<td>Neuroaxis radiation, temozolomide</td>
<td>5</td>
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<tr>
<td>17 (F)</td>
<td>LP vision in right eye, bilateral VI NP, right III NP, No papilledema</td>
<td>—</td>
<td>VPS, BMB</td>
<td>Yes</td>
<td>Steroids</td>
<td>Neuroaxis radiation, temozolomide</td>
<td>15</td>
</tr>
</tbody>
</table>

BMB, brain meningeal biopsy; F, female; HM, hand motions; ICP, intracranial pressure; LE, left eye; LP, light perception; M, male; NP, nerve palsy; RE, right eye; SMB, spinal meningeal biopsy; TB, tuberculosis; VPS, ventriculoperitoneal shunt.

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MRI Restricted Diffusion in Lymphomatous Optic Neuropathy

Padmaja Sudhakar, MD, Francisco Rivas Rodriguez, MD, Jonathan D. Trobe, MD

Abstract: Restricted diffusion in the optic nerve detected with MRI has been previously reported in infarction and inflammation but not in infiltrative neoplasm. We report a 44-year-old man with recently diagnosed non-Hodgkin B-cell lymphoma who developed an acute left optic neuropathy. MRI showed no evidence of brain parenchymal or meningeal lymphoma but did show restricted diffusion in the intraorbital portion of the affected optic nerve. Despite treatment with corticosteroid, standard chemotherapy, and orbital X-irradiation, visual function did not improve. The restricted diffusion persisted on a follow-up MRI performed 4 months after the onset, a phenomenon that is atypical for infarction. Perhaps, this persisting imaging abnormality in lymphomatous optic neuropathy reflects the dense cellularity of the neoplasm.

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Diffusion-weighted imaging (DWI) has been largely applied to the diagnosis of acute cerebral infarction (1). Restricted diffusion on DWI has also been noted in brain parenchymal lymphomas and other brain tumors (2–5). Although this neuroimaging finding has been reported in ischemic and inflammatory optic neuropathies (6–14), it has not previously been reported in lymphomatous optic neuropathy. We describe such a case.

CASE REPORT

A 44-year-old man presented with sudden painful loss of vision in the left eye for 1-day duration. Four months earlier, he had been diagnosed with non-Hodgkin B-cell lymphoma following biopsy of a retroperitoneal mass. He had completed 4 of 6 cycles of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (CHOP) chemotherapy. Precontrast brain CT and complete blood counts obtained at the referring hospital after the vision loss were normal.

On our examination, visual acuity was 20/20 in the right eye and no light perception in the left eye. There were no ocular adnexal abnormalities. There was tenderness to palpation of the left eye. Pupils were equal in size with a left relative afferent pupillary defect. Ocular movements were full, and eyes were aligned. The visual field was full to finger counting in the right eye. Slit-lamp biomicroscopy and intraocular pressures were normal in both the eyes. Ophthalmoscopy of the right eye was normal and disclosed mild swelling of the optic disc of the left eye. There were no other abnormalities on examination.

MRI of the brain and orbits was performed with a 1.5-T Achieva magnetic resonance system (Philips Medical Systems, Best, the Netherlands) using an 8-channel SENSE head coil and included the following pulse sequences: precontrast and postcontrast T1 fat saturated spin echo axial and coronal (time to recovery [TR]: 600 milliseconds, time to echo [TE]: 10 milliseconds, slice thickness 3 mm, with no interslice gap on axial and interslice gap 0.5 mm on coronal, matrix 336 × 165 axial and 256 × 165 coronal), T2 fat saturated spin echo coronal (TR: 3,500 milliseconds, TE: 120 milliseconds, slice thickness 3 mm, with 0.5 mm interslice gap on axial and interslice gap 0.5 mm on coronal, matrix 336 × 165 axial and 256 × 165 coronal), T2 fat saturated spin echo coronal (TR: 1,200 milliseconds, TE: 10 milliseconds, slice thickness 3 mm, with 0.5 mm interslice gap on axial and interslice gap 0.5 mm on coronal, matrix 256 × 130), and FLAIR (TR: 11,000 milliseconds, TE: 140 milliseconds, slice thickness 5 mm, interslice gap 1 mm, matrix 288 × 160). Gadolinium pertechnetate 0.2 mL/kg was administered intravenously.

Diffusion imaging data were obtained using an echo-planar single-shot technique with the shortest TR, 80-millisecond TE, and a b value of 1,000 s/mm². The data were recorded on a 128 × 256 matrix and were zero-filled for a final resolution of 256 × 256. Axial slices with 6-mm slice thickness with no interslice gap were obtained. A SENSE P factor of 3 was used.
Brain and orbit MRI showed no parenchymal or meningeal abnormalities, but the left intraorbital optic nerve showed increased T2 signal intensity, thickening, and minimal enhancement (Fig. 1A, B). There was high signal on DWI and a corresponding area of darkness on the apparent diffusion coefficient (ADC) map (Fig. 1C–E). The ADC values were $0.590 \times 10^{-3}$ mm$^2$/s in the affected left optic nerve and $0.974 \times 10^{-3}$ mm$^2$/s in the fellow (unaffected) optic nerve. We found an average ADC value of $1.293 \times 10^{-3}$ mm$^2$/s in 10 right optic nerves and an average ADC value of $1.109 \times 10^{-3}$ mm$^2$/s in 10 left optic nerves of patients with neurologic symptoms but no manifestations of optic neuropathy. The calculations confirmed restricted diffusion in the affected left optic nerve.

Cerebrospinal fluid (CSF) on lumbar puncture showed glucose: 53 mg/dL (normal: 50–70 mg/dL), protein:100 mg/dL (normal:15–45 mg/dL), and 22 white cells per cubic millimeter (68% lymphocytes). CSF flow cytometry and cytology were positive for a mature B-cell neoplasm, confirming the diagnosis of lymphomatous meningitis.

We attributed the optic neuropathy to lymphomatous infiltration and treated the patient with 1 gm of methylprednisolone per day for 3 days followed by prednisone at 1 mg/kg/day for 14 days.

Previously obtained head, neck, and maxillofacial CT and chest CT were unremarkable. Abdominal and pelvic CT revealed a large retroperitoneal mass extending from the celiac axis to the iliac bifurcation. Positron emission tomography (PET) showed extensive metastatic disease involving the axial bones, lymph nodes, kidneys, adrenals, and the right testis. On review, the core biopsy of the abdominal mass showed abnormal lymphoid cells with high mitotic activity. Fluorescent in situ hybridization analysis revealed an 8;14 translocation consistent with Burkitt lymphoma. Repeat chest, abdomen, and pelvic CT and PET scan demonstrated a decrease in size of the previously seen lesions with no new areas of involvement.

The patient underwent 4 cycles of high-dose intravenous methotrexate (3,500 mg/m$^2$), cytarabine (2,000 mg/m$^2$), rituximab (375 mg/m$^2$), together with intrathecal methotrexate and intrathecal cytarabine on days 2 and 8. After completion of chemotherapy, he underwent right orchectomy and radiation to the left orbit and left scrotum.

Within 5 weeks, the left optic disc became pale. Vision never improved. The right eye maintained normal visual function.

MRI obtained 4 months after the presentation showed that the previously observed enhancement of the retrobulbar fat within the left orbit and the patchy enhancement of the left optic nerve was less intense than that in the prior study. However, it still showed an ADC value of $0.465 \times 10^{-3}$ mm$^2$/s in the left optic nerve and $1.38 \times 10^{-3}$ mm$^2$/s in the right optic nerve (Fig. 2A–C), indicating persistent restricted diffusion in the left optic nerve.

Multiple CSF studies obtained after the initiation of chemotherapy remained negative for neoplasm.

**FIG. 1.** MRI performed at presentation. 
A. Precontrast T1 axial scan demonstrating high signal in the left intraconal space (arrow). 
B. Postcontrast T1 axial image showing mild enhancement of the left intraorbital optic nerve (arrow) and intraconal fat. 
C. Axial DWI reveals high signal in the left intraorbital optic nerve (arrow). 
D. Axial ADC map demonstrating a corresponding region of darkness (arrow). 
E. Axial exponential DWI showing a corresponding region of brightness, as expected with restricted diffusion (arrow).
DISCUSSION

Burkitt lymphoma in our patient infiltrated the left optic nerve and produced persistent restricted diffusion on DWI. To our knowledge, this is the first reported case of such a phenomenon.

DWI is based on the Brownian motion of unbound water molecules in the extracellular space (1). It quantifies the diffusion of water molecules with a value known as apparent diffusion coefficient (ADC). Compromise of the extracellular space following cellular swelling in infarction (1,6) and the dense cellular packing typical of brain tumors restrict motion of extracellular water and produce restricted diffusion (3,15).

DWI has shown restricted diffusion in 8 cases of optic nerve ischemia (6–12,14) and in 1 case of optic perineuritis (13) but not in neoplastic infiltration. The first reported case described a patient with bilateral posterior ischemic optic neuropathy attributed to hypotension in cardiac bypass surgery. Restricted diffusion was seen within both intraorbital optic nerves on an MRI study obtained 4 days after vision loss (6). Follow-up MRI was not obtained.

The second reported case described a 56-year-old woman with nonarteritic anterior ischemic optic neuropathy (7). MRI brain obtained within 2 weeks of visual loss showed restricted diffusion within the left intraorbital optic nerve. ADC was relatively decreased by 46% in the left optic nerve. Follow-up imaging was not done.

The third reported case showed restricted diffusion in both optic nerves in a patient with ischemic optic neuropathy attributed to thombocytopenia (8).

The fourth case involved a patient with bilateral cavernous sinus thrombosis who demonstrated restricted diffusion in both intraorbital optic nerves on MRI obtained within 2 weeks of visual loss (9). The ADC values within the affected optic nerves measured 0.168–0.744 × 10⁻³ mm²/s compared to an ADC of 0.833–1.178 × 10⁻³ mm²/s seen within the normal optic nerves. No follow-up imaging study was done.

Three case reports have documented restricted diffusion in optic nerve infarction secondary to rhinocerebral mucormycosis. The first showed restricted diffusion in the distal right intraorbital optic nerve on an MRI obtained within 6 days of vision loss (10). The restricted diffusion became more apparent on an MRI obtained 15 days later. The second showed restricted diffusion in the distal left optic nerve on an MRI obtained within a few days of vision loss with an ADC value of 0.635 × 10⁻³ mm²/s (11). Both patients died within a few days of losing vision. In the third case of mucormycosis, a 29-year-old man suffered right eye vision loss from ophthalmic artery, cavernous sinus, and superior ophthalmic vein occlusion (12). DWI obtained within 2 days of vision loss showed restricted diffusion not only in the right intraorbital optic nerve (ADC of 0.471 × 10⁻³ mm²/s in the right eye and 1.663 × 10⁻³ mm²/s in the left eye) but also in the retina (ADC of 1.84 × 10⁻³ mm²/s in the right retina and 2.60 × 10⁻³ mm²/s in the left retina). Follow-up MRI obtained within 20 days of symptom onset revealed complete disappearance of these signal changes.

Restricted diffusion was reported in the proximal intraorbital segment of the right optic nerve in a 4-year-old healthy girl who developed central retinal artery and vein occlusion from optic perineuritis (13). MRI obtained within few days of vision loss showed an enhancing and thickened right optic nerve and high T2 signal in the intracanal fat surrounding the optic nerve, together with restricted diffusion in the proximal right intraorbital optic nerve. Imaging features were similar to those of our patient. Follow-up MRI obtained 4 months later documented the disappearance of restricted diffusion and partial reversal of optic nerve thickening.

Restricted diffusion was reported in the left intraorbital optic nerve in a patient with ophthalmic artery occlusion following fat autotransplantation to the forehead for soft tissue augmentation of face (14). The MRI obtained on the third postoperative day showed subtle hyperintensity on DWI in the left middle cerebral arterial territory and left optic nerve (ADC value of 0.272 × 10⁻³ mm²/s in left optic nerve and 1.46 × 10⁻³ mm²/s in the right optic nerve). The MRI obtained on the fourth postoperative day showed more pronounced restricted diffusion in the left optic nerve (ADC of 0.237 × 10⁻³ mm²/s in the left and 1.26 × 10⁻³ mm²/s in the right). No follow-up imaging was obtained.

Our case is unusual in that the restricted diffusion persisted for at least 4 months from the onset of optic neuropathy, unlike the pattern seen in cerebral infarction, where it disappears within 7–10 days (1). Follow-up
imaging has not been consistently performed in the reported cases of restricted diffusion of the optic nerve. Two case reports of optic nerve infarction have documented disappearance of restricted diffusion on follow-up DWI (12,13). In one, restricted diffusion had disappeared within 20 days of symptom onset (12), and in the other, disappearance was documented on DWI obtained 4 months later (13).

We offer 2 explanations for persistent restricted diffusion in our patient. Perhaps, it can be attributed to the high cellularity of Burkitt lymphoma, although lymphoma cells were absent from the CSF on repeated lumbar punctures after the treatment. Previous studies have documented the presence of restricted diffusion with low ADC values in central nervous system lymphomas of B- and T-cell type (2–5,15–19). The high cellularity of lymphoma decreases the extracellular space and restricts the motion of extracellular water leading to restricted diffusion on MRI. The higher the cellularity, the lower the ADC value (3–5,15,16). In a DWI study of intracerebral masses, lymphoma was found to have higher cellularity on histopathology and correspondingly lower ADC values (average 0.58 × 10⁻³ mm²/s) on DWI than gliomas (average ADC 1.14 × 10⁻³ mm²/s) and metastatic cancers (average ADC 1.03 × 10⁻³ mm²/s) (5).

Other studies have shown similar results (3,4,19,20). One study (21) indicated that lymphomas with high cellularity and low ADC values tended to be relatively refractory to chemotherapy. The other postulated mechanism for restricted diffusion in brain parenchymal lymphoma is the increased viscosity characteristic of necrotic lymphomas (15).

Prior studies have documented that lymphoma in the orbit (but not involving the optic nerve) restricts diffusion more than other orbital processes (22,23). In a study that compared DWI intensities, ADC values, and ADC ratios of orbital cellulitis, orbital inflammatory syndrome, and conjunctival, eyelid, and extraconal lymphomas, more restricted diffusion with lower ADC values was found in lymphomas than in the other entities (22).

Given that none of the reported patients who have had restricted diffusion in the optic nerve have recovered vision, this imaging abnormality appears to augur a poor visual outcome, even in inflammatory or neoplastic conditions.

REFERENCES

Undiagnosed Papilledema in a Morbidly Obese Patient Population: A Prospective Study

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Background: Idiopathic intracranial hypertension (IIH) is a rare condition that can lead to significant morbidity from visual loss. The cause of IIH is unknown, but IIH is known to be associated with obesity. Obese patients may be at particularly high risk for suffering vision loss from IIH. The purpose of the present study is to determine the prevalence of undiagnosed or asymptomatic papilledema in a population of morbidly obese individuals and to determine if these patients should undergo routine screening for papilledema.

Methods: Patients presenting to the UC Davis Bariatric Surgery Clinic between February 2008 and January 2011 who met the National Institutes of Health criteria for bariatric surgery were invited to participate in the study. Those patients who met the inclusion criteria and consented to the study were included. Participants were screened for IIH by nonmydriatic fundus photographs and by concerning symptoms prompting direct referral for neuro-ophthalmologic evaluation. Images were reviewed by a neuro-ophthalmologist, and patients with suspicious optic discs underwent neuro-ophthalmologic evaluation. Patients with findings consistent with IIH were sent for neurological evaluation.

Results: A total of 606 patients with an average body mass index of 47 kg/m² were included in the study. Seventeen of these patients had photographic optic disc findings or symptoms suspicious for IIH. Seven of these patients did not have disc edema on clinical examination. Six patients were not evaluated in the clinic. Four of the 17 patients had subtle optic disc edema confirmed by clinical evaluation and were referred for full neurological workup. These 4 patients had normal neuroimaging, 3 of whom underwent lumbar punctures with borderline high opening pressures. All 4 patients had unremarkable visual field examinations. Fundus abnormalities other than optic disc edema were discovered in 33 patients.

Conclusion: Our study suggests that in a morbidly obese patient population, papilledema with significant visual loss is rare. Routine screening with fundus photography of morbidly obese patients likely is not warranted.


Idiopathic intracranial hypertension (IIH or pseudotumor cerebri) is a rare neurological disorder in which cerebrospinal fluid (CSF) pressure is elevated, leading to papilledema and visual disturbances. Patients present with a variety of symptoms, including transient visual obscurations (TVOs), blurred vision, tinnitus, diplopia, or headaches (1–4). The etiology of IIH is unknown, and the diagnosis of IIH is determined by a set of criteria that has served as the standard for IIH diagnosis (modified Dandy criteria) (5). These criteria include 1) signs and symptoms of increased intracranial pressure, 2) normal neuroimaging, 3) absence of focal neurological signs aside from cranial nerve VI paresis, and 4) elevated CSF pressure with normal CSF composition.

IIH is of concern to ophthalmologists and neurologists, as untreated disease can lead to significant morbidity from visual loss, including visual field defects and visual acuity loss, which in some cases is severe and permanent (6–9). Up to 25% of patients with IIH may be asymptomatic (10) that may delay diagnosis, leading to higher risk of permanent visual loss. Thus, it may be prudent to screen patients at the highest risk for IIH to prevent the development of this blinding disorder.

Screening of the general population is unlikely to be cost-effective, as IIH is rare in the general population,
occurring with an annual incidence in the order of 1 to 2 per 100,000 (11–14). While obesity has not been shown to be a cause of IIH, obesity is clearly associated with IIH (3,15), and the incidence of IIH rises to 20 per 100,000 in obese females (11,12). As the prevalence of obesity has increased in the United States, defining the association between obesity and IIH has become increasingly more urgent. Recent updates from the Centers for Disease Control and Prevention place the percentage of obese individuals in the United States more than 30% (16). The percentage of morbidly obese individuals (body mass index [BMI] >40 kg/m²) is estimated to be roughly 6% (16). Interestingly, the risk of IIH increases with increasing BMI (17), and morbidly obese patients with IIH may have even worse visual outcomes (18). Thus, morbidly obese individuals may be at particularly high risk for severe and permanent visual loss from IIH.

In this study, morbidly obese patients presenting for bariatric surgery evaluation at UC Davis were screened for the presence of undiagnosed or asymptomatic papilledema. The goal of our study was to determine if screening morbidly obese patients for IIH is a worthwhile endeavor and to gain insight into the association of IIH with obesity.

**METHODS**

The study design was approved by the University of California, Davis, Institutional Review Board. Patients between the age of 18 and 65 years who presented to the UC Davis Bariatric Surgery Program between February 2008 and January 2011 and met the National Institutes of Health requirements for bariatric surgery (19) were asked to participate in the study (Table 1). All patients presenting for evaluation were questioned about headaches and visual symptoms, but patients who consented to the study were asked to fill out a screening questionnaire (Table 2) and had nonmydriatic fundus photographs taken (Nidek nonmydriatic auto fundus camera, AFC 210 camera [Nidek Inc., Fremont, CA]). Patients were excluded if they had a preexisting diagnosis of IIH or if 1 or both of the fundus photographs were inadequate for interpretation. There were no monoculc patients in this population.

Patients who had at least 1 optic disc suspicious for edema were referred for neuro-ophthalmic evaluation. One patient had suspicious symptoms based on screening questions but did not have fundus photographs taken due to unavailability of the camera. This patient was also referred for neuro-ophthalmic testing (Patient P1) (Table 6). This included visual fields with automated perimetry (automated visual fields, SITA-standard 24-2), optic nerve and macula optical coherence tomography (OCT; Stratus [Carl Zeiss Meditec, Inc., Dublin, CA]), and fundus photography. Optic nerve images were graded for papilledema according to the modified Frisén scale (20,21). All of this information was used to diagnose optic disc edema by a single neuro-ophthalmologist

<table>
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<tr>
<th>TABLE 1. National Institutes of Health requirements for bariatric surgery</th>
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<tr>
<td>• 100 pounds or more above ideal body weight or a BMI of 40 kg/m² or greater</td>
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<tr>
<td>• BMI of 35 kg/m² or greater with 1 or more obesity-related health conditions</td>
</tr>
<tr>
<td>• High risk for obesity-associated morbidity or mortality</td>
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<td>• Previous failed weight loss attempts involving an integrated nonsurgical weight loss program, including dietary modification, behavioral support, and appropriate exercise</td>
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<tr>
<td>• Possession of appropriate motivation and psychological stability to understand risks and benefits of the procedure as well as the commitment to lifelong postoperative lifestyle changes and medical surveillance</td>
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Adapted from the Evidence Report of the National Institutes of Health (19).

(J.L.K.) and ophthalmology residents (C.M.K, D.G.C). Patients with confirmed disc edema underwent neuro-imaging and were referred to neurology for evaluation and lumbar puncture. Final diagnosis and treatment of IIH was determined by the Neurology Department at UC Davis. The diagnosis of IIH did not preclude patients from undergoing bariatric surgery.

**RESULTS**

From February 2008 to January 2011, 1,148 patients presented for evaluation for bariatric surgery. Of the 1,148 patients, 647 met the initial inclusion criteria and consented to the study. Of the excluded patients, 7 reported having a previous diagnosis of IIH. Those patients who declined enrollment did so for various reasons, including history of migraine headache, photophobia, mobility limitations preventing appropriate positioning for the

<table>
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<th>TABLE 2. Screening questionnaire for study enrollment</th>
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<tr>
<td><strong>1A:</strong> Have you ever been diagnosed or treated for a condition called “Idiopathic Intracranial Hypertension” (IIH) or “Pseudotumor Cerebri? (PTC)”</td>
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<tr>
<td><strong>1B:</strong> If NO, have you ever heard of a condition called IIH or PTC, which is caused by high pressures in the brain?</td>
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<tr>
<td><strong>2:</strong> Do you ever have episodes of blurry vision or loss of vision? (that fade in and out and may last less than a minute)</td>
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<tr>
<td><strong>3:</strong> Have you had a new onset of frequent headaches in the past year?</td>
</tr>
<tr>
<td><strong>4:</strong> Have you had a new onset of frequent episodes of nausea this past year?</td>
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<tr>
<td><strong>5:</strong> Have you had a new onset of episodes of double vision?</td>
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fundus photography, and time constraints. Patients with migraine headache generally declined participation due to fear that the flash of the camera would trigger a migraine and were not further evaluated.

Because fundus photographs were inadequate for evaluation in 41 patients, a total of 606 patients were included in the study. Seventy-seven percent of these patients were women, and the average age was 45.3 years. The average BMI was 47.5 kg/m^2, which is considered morbidly obese. Demographics of these patients are shown in Table 3.

Of the 606 patients, 17 were identified on initial screening (either with photographs or with screening questions) as suspicious for having IIH and 11 underwent neuro-ophthalmic evaluation (Table 4). The patients who were not evaluated either failed to return at least 3 phone calls or declined evaluation for other reasons. Patients who declined evaluation were educated on the risks of their decisions.

Of the 11 patients who were evaluated, 7 were deemed not to have true optic disc edema (Table 5). The results of these 7 patients were as follows. Two patients had mildly blurred disc margins on the screening photographs but were not evaluated clinically until 2 and 6 months following bariatric surgery. In both the cases, optic disc appearance was unchanged compared to the screening photographs, and the nerves were deemed to be a congenitally full and a variant of normal. One patient had prior photographs from 2005 that were identical to those taken in 2009. One patient was diagnosed with a hyaloid remnant and 1 with nonarteritic anterior ischemic optic neuropathy. The remaining 2 patients were deemed to have normal optic discs on clinical examination.

Four of the 11 patients had optic disc edema (Table 5). None of these patients had ever been diagnosed with IIH nor were they familiar with the disease. Two of these patients (P2 and P3) had no symptoms of IIH (Table 6). One patient (P3) reported frequent severe headache associated with nausea but no visual symptoms. One patient (P1) reported previous episodes of diplopia, TVOs, and frequent severe headache. All 4 patients were women, and all had mild (Frisen stage 1) optic disc edema. All had fundus photographs and corresponding OCT images (Fig. 1). All 4 patients had visual acuity of 20/20 bilaterally without detectible visual field changes. One of these patients (P1) was evaluated on a day where the nonmydriatic screening camera was unavailable, but the bariatric surgeons were suspicious of IIH, given the patient’s severe headache symptoms. Patient P4 declined lumbar puncture. The other 3 patients had lumbar punctures performed by interventional radiology in the prone position rather than in the lateral decubitus position. Neuroimaging of these 4 patients did not identify an underlying cause for optic nerve edema and was consistent with a diagnosis of IIH. However, only 2 patients (Cases 1 and 2) had a magnetic resonance venography.

**TABLE 3.** Demographics of morbidly obese patients

| Number of patients asked to participate | 1148 |
| Number of patients meeting initial criteria and consented to the study | 647 |
| Number of patients excluded due to poor quality photographs | 41 |
| Number of study participants | 606 |
| Male, n (%) | 142 (23) |
| Female, n (%) | 464 (77) |
| Average BMI, kg/m^2 | 47.5 |
| Age of participants (range), yr | 45.3 (18–65) |
| Ethnicity of participants |
| Caucasian | 445 |
| Hispanic | 77 |
| African American | 62 |
| Asian | 4 |
| Pacific Islander | 4 |
| Native American | 4 |
| East Indian | 3 |
| Middle Eastern | 1 |
| Other/decline to state | 6 |

**TABLE 4.** Test results of morbidly obese study patients

| Total patients enrolled | 606 |
| Normal screening photographs, n (%) | 556 (91.7) |
| Patients with one or both optic discs suspicious for edema, n (%) | 16 (2.6) |
| Abnormalities other than possible optic disc edema, n (%) | 33 (5.4) |
| Patients with suspicious symptoms only (no photographs available), n (%) | 1 (0.2) |

**TABLE 5.** Results of patients with suspicious optic nerves

| Number of patients with suspicious nerves | 17 |
| Number of patients evaluated | 11 |
| Patients evaluated in clinic without optic disc edema |
| Normal nerves | 5* |
| Hyaloid remnant | 1 |
| Nonarteritic anterior ischemic optic neuropathy | 1 |
| Patients evaluated in clinic with mild optic disc edema | 4 |

*This includes 2 patients with mild blurring that was unchanged several months after surgery and 1 patient for whom photographs from 2005 were available and demonstrated no change in appearance.

DISCUSSION

The diagnosis of IIH is traditionally made if the clinical findings meet the modified Dandy criteria (5). Of the

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<tr>
<th>Patient</th>
<th>Best-Corrected Visual Acuity</th>
<th>Symptoms</th>
<th>Intraocular Pressure (mm Hg)</th>
<th>Color Vision (H-R-R)</th>
<th>Automated Visual Fields*</th>
<th>Optic Disc Edema Stage (Frisén)</th>
<th>Neuroimaging</th>
<th>Lumbar Puncture Opening Pressure (cm H₂O)†</th>
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<tr>
<td>P1</td>
<td>OD 20/20; OS 20/20</td>
<td>Severe headaches and nausea</td>
<td>OD 18; OS 15</td>
<td>OD 5/6; OS 5/6</td>
<td>Normal</td>
<td>1</td>
<td>MRI/MRA: normal</td>
<td>32</td>
</tr>
<tr>
<td>P2</td>
<td>OD 20/20; OS 20/20</td>
<td>None</td>
<td>OD 12; OS 12</td>
<td>OD 5/6; OS 5/6</td>
<td>Inconsistent</td>
<td>1</td>
<td>MRI/MRV: normal</td>
<td>24</td>
</tr>
<tr>
<td>P3</td>
<td>OD 20/20; OS 20/20</td>
<td>None</td>
<td>OD 20; OS 16</td>
<td>Not tested</td>
<td>Normal</td>
<td>1</td>
<td>MRI: normal aside from increased fluid in optic nerve sheath§</td>
<td>25</td>
</tr>
<tr>
<td>P4</td>
<td>OD 20/20; OS 20/20</td>
<td>Diplopia, headaches, and TVOs</td>
<td>OD 15; OS 15</td>
<td>6/6; 6/6</td>
<td>Normal</td>
<td>1</td>
<td>MRI: normal§</td>
<td>Not done</td>
</tr>
</tbody>
</table>

*Automated visual fields with SITA-standard 24-2 progress.
†In all cases, lumbar punctures were performed by interventional radiology under fluoroscopy, with the patient in the prone position.
‡MRA was normal; MRV showed “possible narrowing or turbulence in the transverse sinus sigmoid junctions and in the lower superior sagittal sinus.”
§MRV was not done. MRI showed no intensity changes to suggest venous thrombosis.
H-R-R, Hardy–Rand–Rittler color plates; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; OD, right eye; OS, left eye; TVO, transient visual obscuration.
606 patients, 3 (0.50%) (Patient P1, P2 and P3) met these criteria for IIH. This number does not include Patient P4 who declined lumbar puncture. All cases identified in the current study had very mild papilledema, which was not visually significant at the time of diagnosis. Whether these patients would have progressed to more severe papilledema is unknown.

While obesity is clearly associated with IIH (2,15), the relationship between obesity and IIH remains complex and is not fully understood. One study even suggested that IIH may have a role in causing obesity (22). Several reports support the notion that recent weight gain contributes to the development of IIH (17,23). Daniels et al (17) found that weight gain in previously nonobese patients was as much of a risk factor for development of IIH as obesity itself. The fact that weight loss (2), including due to bariatric surgery (24,25), improves or resolves signs and symptoms of IIH supports the strong association of obesity and IIH. Yet, it is difficult to be certain of a direct causal link between changes in weight and IIH or possibly the relationship is due to the myriad of metabolic and inflammatory changes that occur with obesity, weight gain, and weight loss (3).

Our study examined a large population of morbidly obese patients and found that none had papilledema with significant visual loss. Whether the 6 patients with suspicious optic nerves who were not evaluated in clinic could have undiagnosed IIH is unknown. However, all 6 of these patients had mild optic disc edema (stage 1) on screening photographs (Fig. 2); therefore, it seems unlikely that any cases of papilledema with significant visual loss were excluded. One interpretation of these data is that obesity alone is not a direct causal factor in the development of IIH. Because our study population comprised chronically obese patients, we are unable to assess if recent weight gain is a major risk factor for developing IIH. Previous studies suggest that if this is the case, then treatment with aggressive weight loss, including bariatric surgery, may be beneficial (2,25).

This study has several limitations. First, the large body habitus of our patients precluded in-office lumbar punctures in the lateral decubitus position. Normative data for opening pressures are known for the lateral decubitus position, but similar normative data do not exist for lumbar punctures performed in the prone position (26). Therefore, it is unclear how to interpret these opening pressure values.

We did not analyze the comorbidities of our patients. Obesity is associated with numerous chronic medical conditions that may affect the development of IIH, including obstructive sleep apnea, hypertension, diabetes mellitus, and hypercoagulability. Further research into this

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**FIG. 1.** Fundus photographs of Patient 1 demonstrating bilateral stage 1 optic disc edema. Corresponding OCT images (Stratus) are shown below the photographs, confirming mildly increased retinal nerve fiber layer thickness.

**FIG. 2.** Screening fundus photographs from 1 of the 6 patients who was not evaluated in the clinic. (This is a representative example. Based on these screening photographs, we recommended the patient be seen for a full neuro-ophthalmologic evaluation, but this patient declined evaluation.)
area is ongoing. Finally, only 2 of the 4 patients with mild optic disc edema had magnetic resonance venograms. The magnetic resonance venogram for patient P1 was inconclusive. The other 2 patients had MRI only. It is possible that these imaging studies could have missed cerebral venous thromboses causing papilledema.

To our knowledge, this is the first prospective study evaluating the prevalence of previously undiagnosed IIH in morbidly obese patients. We found that, in this patient population, asymptomatic or previously undiagnosed papilledema with significant visual loss is extremely low. Based on our results, routine screening for papilledema with nonmydriatic fundus photographs for asymptomatic obese patients is likely not warranted. However, bariatric surgeons should be vigilant in screening for any symptoms consistent with IIH and refer these patients promptly for neuroophthalmic evaluation.

ACKNOWLEDGMENT

The authors thank Raymond Kong for his assistance with creating the figures.

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The Berlin Questionnaire Screens for Obstructive Sleep Apnea in Idiopathic Intracranial Hypertension

Matthew J. Thurtell, MBBS, FRACP, Beau B. Bruce, MD, David B. Rye, MD, Nancy J. Newman, MD, Valerie Biousse, MD

Background: Obstructive sleep apnea (OSA) may be associated with idiopathic intracranial hypertension (IIH), a disorder most commonly occurring in young obese women. Because polysomnography, the standard test for diagnosing OSA, is expensive and time consuming, questionnaires have been developed to identify persons with OSA. The Berlin questionnaire (BQ) reliably identifies middle-aged and older persons in the community who are at high-risk for OSA. We aimed to validate the BQ as a screening tool for OSA in IIH patients.

Methods: Patients with newly diagnosed IIH completed the BQ and then underwent diagnostic polysomnography. The BQ was scored as high or low risk for OSA, and the diagnosis of OSA was based on polysomnography findings. OSA was defined as an apnea-hypopnea index of at least 5 on polysomnography.

Results: Thirty patients were evaluated (24 women; 15 white and 15 black; age, 16–54 years [median, 32 years]; body mass index, 27.3–51.7 kg/m² [median, 39.8 kg/m²]). Twenty patients (66.7%) had a high-risk BQ score and 18 (60%) exhibited OSA. Fifteen of 20 (75%) with a high-risk BQ score had OSA, while 3 of 10 (30%) with a low-risk score had OSA (Fisher test, \( P = 0.045 \)). The sensitivity and specificity of the BQ for OSA in IIH patients were 83% and 58%, respectively, whereas the positive predictive value was 75%.

Conclusion: A low-risk BQ score identifies IIH patients who are unlikely to have OSA. Polysomnography should be considered in those with a high-risk score.

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Obstructive sleep apnea (OSA) is a common condition in which there are intermittent partial (viz, hypopneas) and complete (viz, apneas) limitations in airflow, with associated hypoxia and sympathetic arousals during sleep (1,2). It is associated with obesity and older age, is more common in men, and, when left untreated, results in increased cardiovascular morbidity and mortality (1–3). Polysomnography is the gold standard test for OSA diagnosis, but requires overnight evaluation (4). The Berlin questionnaire (BQ), which includes questions about snoring, daytime somnolence, body mass index (BMI), and hypertension, is a brief and validated screening tool that identifies persons in the community who are at high risk for OSA (5).

OSA is thought to be associated with idiopathic intracranial hypertension (IIH) (6). Although the BQ has been used as a screening tool for OSA in prior IIH studies (7), validation studies of the BQ have only been performed in middle-aged and older adults living in the community, whereas IIH most often occurs in young obese women (5). Because outcomes may be worse in IIH patients who have OSA (3,8), we obtained diagnostic polysomnography on newly diagnosed IIH patients. We concurrently administered the BQ to evaluate its validity as a screening tool for OSA in IIH patients.
METHODS

Standard Protocol Approvals and Patient Consents
The study was approved by our institutional review board. As data were collected retrospectively, patients were not required to give written informed consent.

Patients
Since March 2008, all newly diagnosed IIH patients seen in the Neuro-Ophthalmology Unit at our institution have completed the BQ and been referred for overnight polysomnography as part of their evaluation; polysomnography could not be obtained in some patients (e.g., if they declined or did not have medical insurance). We retrospectively included all newly diagnosed patients satisfying the updated modified Dandy criteria for IIH (9) who had completed the BQ and had undergone polysomnography. We excluded patients who were pregnant, were younger than 16 years, had a prior diagnosis of IIH, or had another cause for their increased intracranial pressure.

Berlin Questionnaire
The BQ (Fig. 1) incorporates questions about snoring (category 1), daytime somnolence (category 2), and hypertension and BMI (category 3) (5). The BQ was administered at the time of the patient’s initial visit. When available, the patient’s family or bed partner was asked to confirm the accuracy of responses to the questions about snoring. The overall BQ score was determined, as in previous studies, from the responses to the 3 categories: scores from the first and second categories were positive if the responses indicated frequent symptoms (≥3–4 times/week), whereas the score from the third category was positive if there was a history of hypertension or a BMI >30 kg/m² (5). Patients were scored as being at high risk for OSA if they had a positive score on 2 or more categories, while those who did not were scored as being at low risk (5).

![Image of the Berlin Questionnaire](https://example.com/image.png)

**FIG. 1.** The BQ for OSA (5). The questionnaire incorporates questions about snoring (category 1), daytime somnolence (category 2), and hypertension and BMI (category 3). BQ, Berlin questionnaire; OSA, obstructive sleep apnea; BMI, body mass index.
Polysomnography

All patients had overnight laboratory-based video polysomnography, including electroencephalogram, electro-oculography, surface mentals and anterior tibialis electromyogram, electrocardiogram, respiratory airflow (measured by thermistor) and effort (measured by piezoelectric sensors), and oxyhemoglobin saturation. The presence of apneas and hypopneas was determined using conventional criteria (4). The polysomnographic technologists scoring the study and the board-certified sleep specialists who interpreted the studies were blinded to the results of the BQ. The apnea-hypopnea index (AHI) was then calculated as the average number of apneas and hypopneas per hour. OSA was diagnosed when the AHI was $\geq 5$ (4).

Data Analysis

Univariate analyses were used to summarize the results. The sensitivity and specificity of the BQ for OSA were determined by comparing the number of IIH patients with high-risk and low-risk BQ scores to the number with and without OSA, while the significance of the association between BQ score and OSA was determined using the Fisher exact test.

RESULTS

Patient Demographics

Thirty newly diagnosed IIH patients were included. Twenty-four were women. The median age was 32 years (range, 16–54 years). Fifteen were whites, and 15 were blacks. The median BMI was 39.8 kg/m$^2$ (range, 27.3–51.7 kg/m$^2$). There was no difference in age, race, or BMI between patients who underwent polysomnography and those who did not ($P > 0.18$).

Berlin Questionnaire Scores

Twenty of 30 patients (66.7%) had a high-risk score for OSA on the BQ, while 10 (33.3%) had a low-risk score (Table 1). Sixteen of 24 women (66.7%) and 4 of 6 men (66.7%) had a high-risk score. Eleven of 15 white patients (73.3%) and 9 of 15 black patients (60%) had a high-risk score. Of 30 patients, 17 (56.7%) had a positive score in category 1 of the BQ, 17 (56.7%) had a positive score in category 2, and 28 (93.3%) had a positive score in category 3, in most cases because their BMI was $>30$ kg/m$^2$. Snoring could not be determined in 3 patients (10%), as they did not have a bed partner who could corroborate their perceived absence of snoring.

Polysomnography Results

Eighteen of 30 patients (60%) had OSA (Table 1), with 7 (23.3%) having mild, 4 (13.3%) having moderate, and 7 (23.3%) having severe OSA. Fourteen of 24 women (58.3%) and 4 of 6 men (66.7%) had OSA. Ten of 15 white patients (66.7%) and 8 of 15 black patients (53.3%) had OSA.

Berlin Questionnaire Sensitivity and Specificity

Fifteen of 20 patients (75%) with a high-risk BQ score had polysomnographically verified OSA, whereas 7 of 10 (70%) with a low-risk BQ score did not have OSA (Table 1). The sensitivity of the BQ for OSA in IIH patients was 83.3%, the specificity was 58.3%, the positive predictive value was 75%, and the negative predictive value was 70% (Fisher test, $P = 0.045$).

TABLE 1. Contingency table of OSA determined by polysomnography (AHI $\geq 5$) vs BQ score

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Low risk</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Fisher test: $P = 0.045$. OSA, obstructive sleep apnea; AHI, apnea-hypoxia index.

DISCUSSION

Overnight laboratory-based polysomnography is the gold standard test for diagnosing OSA (4), but given the expense, time requirement, and inconvenience of polysomnography for many patients, it would be preferable to first use a simple and sensitive screening test to determine an IIH patient’s risk for OSA. The BQ can be completed in a few minutes and has been validated as a useful screening tool for identifying persons in the community who are at high-risk for OSA (5). In a large study, 744 community-dwelling adults completed the BQ; similar numbers of men and women were studied, but most were middle-aged or older (48.9 ± 17.5 years, mean ± SD) (5). After completing the BQ, 100 of the participants underwent polysomnography. Fifty-nine of 69 participants (86%) with a high-risk score had OSA, and 7 of 31 (23%) with a low-risk score had OSA. Thus, the sensitivity and specificity of the BQ for identifying OSA were 86% and 77%, respectively (5).

The BQ is not as predictive of OSA in specialized sleep clinics. Indeed, a lower threshold for performing diagnostic polysomnograms on a mixed patient population likely accounts for a lower sensitivity and specificity (68% and 49%, respectively) for identifying OSA in such clinics (10). In contrast to study and sleep clinic populations, IIH patients are typically young. Therefore, it was uncertain whether the BQ would reliably identify IIH patients with OSA (5,10). Because OSA may be associated with IIH (6,8,11,12), and OSA has been shown to increase cardiovascular morbidity and mortality (3), we felt compelled to evaluate all IIH patients for OSA with polysomnography until the BQ was validated in the IIH population.
We routinely administered the BQ and obtained diagnostic polysomnography on newly diagnosed IIH patients and found 83% sensitivity, 58% specificity, and 75% positive predictive value of the BQ for identifying OSA in IIH patients. The frequency of snoring might have been underestimated by the BQ, as several patients lacked a family member or bed partner to confirm the questionnaire responses. Nonetheless, our findings demonstrate that the sensitivity of the BQ in IIH patients is comparable to that observed in older individuals in the general community.

It is important to note that this study was not designed to evaluate for an association between OSA and IIH. Although the majority of our patients had OSA by polysomnography, comparison with age-, sex-, race-, and BMI-matched controls is required to determine if there is any evidence of an association between IIH and OSA.

Our study has several limitations. First, it was retrospective rather than prospective. Yet, all patients were evaluated in a standardized fashion, which should have substantially reduced the biases usually associated with retrospective studies. Second, not all of our IIH patients underwent polysomnography. However, all patients were referred for polysomnography regardless of their perceived risk for OSA, and bias was minimized as much as possible. In addition, there were no differences between the groups of patients who did and did not undergo polysomnography.

Despite these limitations, our study suggests that the BQ is a practical adjunct tool for stratifying IIH patients as to their risk for OSA. Given the significant morbidity associated with OSA, especially in obese individuals, polysomnography should be considered in IIH patients with high-risk BQ scores.

REFERENCES
Comparison of 10-mg Doses of 4-Aminopyridine and 3,4-Diaminopyridine for the Treatment of Downbeat Nystagmus

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Objective: Animal experiments have demonstrated that aminopyridines increase Purkinje cell excitability, and in clinical studies, 4-aminopyridine (4-AP) and 3,4-diaminopyridine (3,4-DAP) improved downbeat nystagmus. In this double-blind, prospective, crossover study, the effects of equivalent doses of 4-AP and 3,4-DAP on the slow-phase velocity (SPV) of downbeat nystagmus were compared.

Methods: Eight patients with downbeat nystagmus due to different etiologies (cerebellar degeneration [n = 1], bilateral vestibulopathy [n = 1], bilateral vestibulopathy and cerebellar degeneration [n = 1], Arnold-Chiari I malformation and cerebellar ataxia [n = 1], cryptogenic cerebellar ataxia [n = 4]) were included. They were randomly assigned to receiving a single capsule of 10 mg of 3,4-DAP or 4-AP followed by 6 days with no medication. One week later, the treatment was switched, that is, 1 single capsule (10 mg) of the other agent. Recordings with 3-dimensional video-oculography were performed before and 45 and 90 minutes after drug administration.

Results: Both medications had a significant effect throughout time (pre vs post 45 vs post 90) (F(2,14) = 8.876; P < 0.01). Following the administration of 3,4-DAP, mean slow velocity decreased from \(-5.68\) /s (pre) to \(-3.29\) /s (post 45) to \(-2.96\) /s (post 90) (pre vs post 45/post 90 P < 0.01). In 4-AP, the mean SPV decreased from \(-6.04\) /s (pre) to \(-1.58\) /s (post 45) to \(-1.21\) /s (post 90) (pre vs post 45/post 90 P < 0.00001). Both after 45 and after 90, the mean SPVs were significantly lower for 4-AP than for 3,4-DAP (P < 0.05). None of the patients reported serious side effects.

Conclusion: Based on these results, 10-mg doses of 4-AP lead to a more pronounced decrease of the SPV of downbeat nystagmus than do equivalent doses of 3,4-DAP.

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Downbeat nystagmus (DBN) is the most frequent type of acquired nystagmus that is present in primary position (1,2). It impairs vision due to vertical oscillopsia (2–4) and frequently leads to postural instability (1–6). DBN is often caused by an identifiable cerebellar patholology, including cerebellar degeneration (7), which affects the flocculus bilaterally (8–10). It has been hypothesized that the bias drift of DBN is caused by a reduced function of the inhibitory, vertical gaze, velocity-sensitive Purkinje cells (PCs) in the cerebellar flocculus (9). Because these cells show a physiological asymmetry, having a preponderance of cells with downward on-directions, their loss leads to disinhibition of neurons in the superior vestibular nucleus and the adjacent Y group and, hence, to spontaneous upward drift (11–13). In primary gaze, this upward drift leads to fast phases that are downward (4,14). This upward-directed drift generally increases in downgaze and decreases or even reverses in upgaze.
Clinical studies have shown that aminopyridines improve DBN (2,6,15–17). In patients with episodic ataxia type 2, aminopyridines also reduce interictal cerebellar ataxia (18) and the frequency of attacks (19). In addition, 3,4-DAP has been used in Lambert-Eaton myasthenic syndrome and 4-AP (in the sustained release form, Ampyra; Biogen Idec, Cambridge, MA) for gait impairment in multiple sclerosis (20–27).

Aminopyridines increase the resting activity and excitability of the PCs, which may restore their inhibitory influence on deep cerebellar nuclei and vestibular nuclei (28). It has also been demonstrated that therapeutic concentrations of 4-aminopyridine restore the diminished precision of pacemaking in PCs of the ataxic P/Q channel mutant mouse by prolonging the action potential and increasing the action potential after hyperpolarization (29).

The effects of 4-AP on the cerebellum were confirmed by a positron emission tomographic study that showed 4-AP increased metabolic activity bilaterally in the cerebellar flocculus (20).

We conducted a double-blind, crossover study to look at the effects of single doses (10 mg) of 4-AP or 3,4-DAP on
the mean slow-phase velocity (SPV) in 8 patients with DBN prior to, 45 minutes after, and 90 minutes after administration. Obtaining our first measurement 45 minutes following the oral administration of the drugs was chosen because prior studies in patients with multiple sclerosis have shown that both drugs are rapidly absorbed with peak serum levels ranging from 20 to 60 minutes after dosing (21). We chose 90 minutes as our second measurement because serum half-life was reported to lie between 1 and 3 hours (21).

**METHODS**

**Patients**

Eight patients with DBN were included in our study (Table 1). Mean duration of DBN was 7.8 years (range, 3–24 years) and patient age ranged from 58 to 76 years (mean, 68 ± 5.93 years). Patients were randomly assigned capsules of 10 mg of 3,4-DAP or 4-AP; they received 1 single capsule of either substance. There was a washout period of 6 days when no medication was given. One week later, the treatment was switched (i.e., they received a single capsule of the other substance). On both days of testing, the patients’ eye movements were recorded prior to the administration of medication and 45 minutes and 90 minutes later. In the intervals between the recordings, patients rested in an upright position.

As in our previous studies (14, 22), all patients underwent a complete clinical examination, including neuro-ophthalmological, neuro-otological, and neurological tests, high-resolution MRI of the brainstem and the cerebellum, electroneystagmography with caloric irrigation, electrocardiography, and hematological tests, including vitamin B12 and magnesium levels. No patient was taking medication that affected the vestibular or ocular motor systems, and DBN was not caused by medication or a metabolic disorder. All patients gave informed consent, and the study was performed in accordance with the Helsinki II Declaration and was approved by the Ethics Committee of the Ludwig-Maximilians University Medical Faculty.

**Recording of Eye Movements**

During the 3 measurement sessions (before medication, 45 minutes after medication, and 90 minutes after medication), patients were monitored in an upright position. A 30-second eye movement recording was made with 3-dimensional video-oculography (GN Otometrics Hortmann Vestlab 100 (GN Store Nord, Ballerup, Denmark), with a 50 Hz sampling rate, 0.1° resolution in horizontal and vertical directions, accuracy of 0.6°, a range of ±30° in the horizontal and vertical directions) (14,23). It took place in the following order (calibration in 8.5° position): 1) gaze straight ahead with fixation turned on; 2) gaze straight ahead in darkness (with no possibility to fixate on a fixation point); 3) 17° rightward gaze; 4) 17° leftward gaze; 5) 17° upward gaze; and 6) 17° downward gaze. The target was projected by laser onto a white background placed 60 cm in front of the patient. For every recording, the chair and head restriction were adjusted so that the target appeared at eye level and the head was fixed in position.

**Monitoring of Side Effects**

Before providing their informed consent, all patients had received information about possible medication side effects. They were asked immediately, 30 minutes, 1 hour, and 2 hours after taking the medication whether they were experiencing any side effects.

**Data Acquisition and Calibration**

Eye position was measured with 3-dimensional video-oculography (23) for 30 seconds. Data were analyzed offline using Matlab (Mathworks, Natick, MA). The calibrated data were low-pass filtered applying a digital Gaussian filter with a bandwidth of 30 Hz, smoothing out higher-frequency components above 30 Hz in the eye position data. The calculated filter coefficients were convolved with the eye position data in Matlab software (Mathworks). Eye velocity was calculated from this smoothed signal by numerical differentiation. Saccades were detected automatically by the software program and manually checked by a trained technician. This was particularly important in patients with a high frequency of saccades. Possible detection errors were corrected manually, and the mean SPV was computed from this data.

**Statistical Data Analysis**

Repeated measurement analysis of variances (Statistica 6.1; Statsoft, Tulsa OK) were carried out along with post hoc Scheffé tests for individual comparisons. SPV of vertical eye movements was the dependent variable. The values of all the following figures were transformed so that DBN indicated by SPV degrees/second (°/s) appears as a negative value on the scale, whereas the absence of DBN appears as a (close to) zero value. The analysis included the following: fixation (=light on) vs viewing in the dark (=light off), medication type (4-AP vs 3,4-DAP), and time (before medication, 45 minutes after medication, 90 minutes after medication).

**RESULTS**

Both medications had a salutary effect on DBN. Representative eye movement recordings are illustrated in Figure 1. The analysis of variance included a comparison between both medications over time (pre vs post 45 minutes vs post 90 minutes). This analysis was significant (P < 0.01) with the F test reaching a value of 8.88 (numerator degrees of freedom = 2, denominator degrees of freedom = 14).

Following the administration of 3,4-DAP, mean SPV decreased from −5.68°/s (pre) to −3.29°/s (post 45) to −2.96°/s (post 90) (with Scheffé post hoc comparisons between pre and...
post 45/post 90; \( P < 0.01 \)). Following the administration of 4-AP, mean SPV decreased from \(-6.04^{\circ}/s\) (pre) to \(-1.58^{\circ}/s\) (post 45) to \(-1.21^{\circ}/s\) (post 90) (with Scheffé post hoc comparisons between pre and post 45; \( P < 0.00001 \), and between pre and post 90; \( P < 0.00001 \)). While the pre-mean SPV measurements of both medications did not significantly differ from each other (\(-6.04^{\circ}/s\) vs \(-5.68^{\circ}/s\; P = 0.97\), both post 45 and post 90 SPV measurements were significantly lower for 4-AP than for 3,4-DAP (\(-1.58^{\circ}/s\) vs \(-3.29^{\circ}/s\) and \(-1.21^{\circ}/s\) vs \(-2.96^{\circ}/s\) with each Scheffé test; \( P < 0.05 \)) (Fig. 2).

**FIG. 1.** Patient 1. Eye movement recording prior to administration and 45 minutes and 90 minutes following administration of 4-aminopyridine (A) and 3,4-diaminopyridine (B).
All patients apart from Cases 2 and 5 responded with a mean SPV decline after the administration of 3,4-DAP. After the administration of 4-AP, Case 2 again did not respond with a decline in mean SPV, while Case 5 showed a reverse from negative mean SPV values (DBN) to positive values (indicating upbeat nystagmus).

Additional significant findings included the effect of time for both medications: pre vs post 45 vs post 90 \((F(1,7) = 10.72; \ P < 0.01)\); individual Scheffe tests between pre and post 45 \((P < 0.01)\), between pre and post 90 \((P < 0.01)\), and between post 45 and post 90 \((P > 0.05)\). DBN also had a lower mean SPV in light \((F(1,7) = 14.14; \ P < 0.01)\).

Fixation on the target (=light on) was associated with an average SPV value of \(-2.23/\mathrm{s}\). No fixation (=light off) was associated with an average SPV value of \(-4.69/\mathrm{s}\).

All 8 patients reported mild paresthesias from 30 minutes to 2 hours after ingestion of both medications. No other side effects were reported.

**DISCUSSION**

It had been previously shown that both 4-AP and 3,4-DAP decrease the mean SPV of DBN \((2,21,23–25)\). It was unclear whether they differ in terms of their treatment efficacy. Therefore, identical single 10-mg doses of both aminopyridines were compared in our double-blind study with crossover design. Our results demonstrate that 4-AP decreased the intensity of DBN significantly more than did 3,4-DAP. This may be due to the different pharmacokinetics and the action of the 2 aminopyridines in blocking cellular potassium channels. Would these results be different if we had observed the effects of 3,4-DAP and 4-AP over a longer period of time? We do not expect a different outcome because both medications reach their peak serum level approximately 60 minutes after oral administration \((21)\). There are conflicting reports that the 2 drugs may have similar half-lives \((21)\) or that 4-AP has a longer half-life than 3,4-DAP \((26,27,30–32)\). In addition, 4-AP has a better ability to cross the blood-brain barrier because it is highly lipid soluble and able to block K+ channels in both the central and peripheral nervous systems \((21,26,27,30–32)\). 3,4-DAP is only soluble in aqueous solution and does not cross the blood-brain barrier easily. It acts primarily to block K+ channels in the peripheral nervous system \((23)\). Given that DBN is a central ocular motor disorder, one would expect 4-AP to have a greater effect on DBN.

With the exception of paresthesias, none of our patients experienced side effects after ingestion of either medication. There were similar complaints following the administration of both medications. This is consistent with previous studies \((2,15–17,21,33–35)\). Not all patients may be eligible for aminopyridines due to prolonged frequency-corrected QT intervals in the electrocardiogram, where potassium-blocking drugs, such as aminopyridines, could lead to dangerous cardiac arrhythmias. As an alternative, one might want to consider behavioral approaches to reduce DBN, for example, to rest in upright head position \((36)\).

Our study was limited in that we only assessed mean SPV as a measure of improvement in DBN. For future studies, it will be important to look at other parameters, including visual acuity, nystagmus amplitude, and nystagmus frequency.

**ACKNOWLEDGMENT**

The authors thank Judy Benson for proofreading the manuscript and all patients for taking part in the study. They also thank Dr Rainer Spiegel and Dr Stefan Glasauer who carried out the statistical analyses and Dr Erich Schneider and by Dr Ales Hahn for providing additional technical and statistical advice (with an emphasis on the 3D video-oculographic device).

**REFERENCES**


Nystagmus and Ataxia Associated With Antiganglioside Antibodies

Seong-Hae Jeong, MD, Jungmoo Nam, MD, Min Jeong Kwon, PhD, Jong Kuk Kim, MD, PhD, Ji Soo Kim, MD, PhD

Background: Antiganglioside antibodies are found in various neurological disorders that constitute a continuum from peripheral neuropathy to encephalitis. However, nystagmus has rarely been described in patients with ataxia associated with antiganglioside antibodies.

Methods: From January 2008 to July 2009, we identified 3 patients with acute ataxia and nystagmus in 2 University Hospitals of Korea, who were found to have anti-GD1b, anti-GM1, or anti-GQ1b antibodies.

Results: In addition to acute ataxia, all 3 patients showed various combinations of nystagmus, which included central positional nystagmus (n = 3), vertical nystagmus (n = 1), and periodic alternating nystagmus (n = 1). The spontaneous and positional nystagmus were mostly detectable only with the elimination of fixation and magnification of the eyes using video goggles. Two patients also exhibited gaze-evoked nystagmus that was noticeable without the aid of video goggles. Patients had serum IgG antibodies to GD1b, GM1, or GQ1b. Cerebrospinal fluid examination, nerve conduction studies, and brain MRI were normal. In all patients, the symptoms and signs resolved over 3–12 months.

Conclusions: Various forms of nystagmus with acute ataxia may be a sole or predominant manifestation of disorders related to antiganglioside antibodies. The nystagmus indicates a central pathology involving the cerebellum or brainstem in this antibody-associated disorder. Antiganglioside antibodies should be measured in patients with nystagmus and acute ataxia of undetermined etiology.

Gangliosides, sialic acids containing glycosphingolipids, are diverse and highly complex molecules located primarily on the plasma membranes of the nervous system (1,2). Gangliosides play important roles in biological functions, such as cellular growth and differentiation, modulation of signal transduction, and immune reactions (3). Antibodies to gangliosides have been found in the neuropathy associated with IgM paraproteinemina (4), multifocal motor neuropathy (5), chronic inflammatory demyelinating polyneuropathy (6), Fisher syndrome, Guillain–Barré syndrome (GBS) (7), and Bickerstaff brainstem encephalitis (8). In particular, GQ1b, GD1b, and GM1 are the antigens frequently recognized by such serum antibodies. Several studies have also reported dense distribution of GQ1b at the dorsal root ganglion and paranodal myelin of the cranial nerves innervating extraocular muscles (9). These findings may explain the frequent observation of ophthalmoplegia and ataxia in patients with anti-GQ1b antibody. Although the distribution of GM1 and GD1b is largely unknown in human central nervous system (10,11), serum antibodies against GM1 or GD1b are frequently detected in autoimmune neuropathies, such as multifocal motor neuropathy, IgM paraproteinemic neuropathy, and GBS. Furthermore, IgG anti-GD1b antibody is closely associated with sensory or cerebellar-type ataxia in patients with GBS (12,13).

Ataxia and ophthalmoplegia have been associated with anti-GQ1b antibody in Fisher syndrome, GBS with ophthalmoplegia, and Bickerstaff brainstem encephalitis (14,15). Also, ophthalmoplegia has been reported in association with anti-GM1 and anti-GD1b IgM antibodies (16,17). However, ocular oscillations have been described only in 2 patients with antiganglioside antibodies. One
patient with sensory dominant polyneuropathy and cerebel-
lar ataxia developed downbeat nystagmus in the presence
of serum IgM protein that specifically bound to GM1,
GD1b, and asialo-GM1 (18). Ocular flutter was reported in
another patient with anti-GQ1b antibody–associated
ataxia and myoclonus (19). We describe nystagmus in
3 patients with autoantibodies against gangliosides GD1b,
GM1, and GQ1b.

METHODS

Subjects
We identified 3 patients with dizziness, nystagmus, and
ataxia in association with antiganglioside antibodies in 2
university hospitals in Korea from January 2008 to July
2009 (Table 1). This study received approval from the
Institutional Review Board of the Seoul National University
Bundang Hospital.

Neurological Evaluation
Patients received a bedside neurological evaluation, in-
cluding spontaneous, gaze-evoked (GEN), head-shaking,
and positional/positioning nystagmus, in addition to rou-
tine neurological testing. Spontaneous and positional/
positioning nystagmus were observed with fixation and
after eliminating fixation and magnifying the eyes using
binocular video goggles (SLMED, Seoul, South Korea).
GEN was induced by fixating on an eccentric target in the
horizontal and vertical directions without using video
goggles. For positional/positioning nystagmus, patients were
asked to look at their knees with their head bent down,
straightened, and turned to either side while sitting. Patients
were also subjected to lying down, turning their head to
either side while supine, straight head hanging, and Dix–
Hallpike maneuvers (20). In 2 patients, eye movements
were also recorded using 3-dimensional video-oculography
(SMI, Teltow, Germany).

Measurements of Antiganglioside Antibodies
Serum samples were obtained from the patients during the
acute phase. The samples were analyzed for the presence of
IgG antibodies against GQ1b, GD1b, and GM1. Detailed
methods on measurement of anti-GQ1b antibody have
been described previously (21). The presence of anti-GD1b
and anti-GM1 antibodies was determined using an enzyme-
linked immunosorbent assay kit (IMMCO Diagnostics, Inc,
Buffalo, NY) according to the manufacturer’s instructions.

RESULTS

Clinical Course
Our patients suffered from dizziness/vertigo and imbalance
that developed either suddenly or over a few days and
improved over several months. Patients were young (age
range = 16–32 years) and in excellent health. Only 1 patient
reported a preceding upper respiratory infection before the
development of dizziness and imbalance (Table 1). In all
patients, the symptoms and signs resolved over 3 to 12
months without specific treatment.

Patterns of Nystagmus
Along with GEN, patients showed central positional nystag-
mus (CPN), upbeat and downbeat nystagmus, or periodic
alternating nystagmus (PAN) (Table 1). With the exception
of CPN in Case 1, the spontaneous and positional nystagmus
were noticeable only with the elimination of fixation and
magnification of the eyes using video goggles. GEN was
present only during horizontal gaze in one patient (Case
2), whereas it was induced during both horizontal and verti-
cal gazes in another patient (Case 1). CPN took various
forms, but 2 patients showed direction-changing positional
nystagmus, apogeotropic in one (Case 1) and geotropic in the
other (Case 3). In Case 2, the spontaneous upbeat nystagmus
changed to downbeat with head bending. Case 2 also showed
evolution of nystagmus from PAN and GEN to CPN and
then to upbeat nystagmus. Case 3 also developed positional
upbeat nystagmus during follow-up.

Antiganglioside Antibodies
Patients showed serum IgG antibodies to GD1b, GM1, or
GQ1b (Table 1). One patient (Case 2) also showed findings

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<th>Patient/ Age/</th>
<th>Preceding Illness</th>
<th>Nystagmus</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
<td></td>
<td>Anti-GD1b</td>
</tr>
<tr>
<td>1/32/F URI</td>
<td>H/V GEN, CPN</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>2/16/M —</td>
<td>PAN, downbeat, upbeat, GEN, CPN</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>3/29/M —</td>
<td>CPN</td>
<td>Positive</td>
<td>Positive</td>
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</tbody>
</table>

Downbeat, downbeat nystagmus; F, female; H/V, horizontal/vertical; M, male; ND, not done; upbeat, upbeat nystagmus; URI, upper respiratory infection.

TABLE 1. Clinical profile of patients with antiganglioside antibodies

suggestive of recent Epstein-Barr virus (EBV) infection (see Report of Cases).

Other Findings

Other than ataxia and nystagmus, patients showed normal neurological examination, except mild bifacial and right arm weakness, and dysarthria in 1 patient (Case 1). All patients had full ocular motility, intact sensory examination, and normal deep tendon reflexes. Cerebrospinal fluid (CSF) examination was performed in 2 patients, and the results were normal. Nerve conduction study (NCS) was also normal in 2 patients. Brain MRI in all patients did not show any abnormality, which would explain their symptoms and signs.

Report of Cases

Case 1

A 32-year-old woman was referred for evaluation of vertigo and imbalance for 2 months. She was treated with a canalith repositioning maneuver for presumed benign paroxysmal positional vertigo (BPPV). Over the following month, her balance worsened and she was unable to sit unaided. The patient then gradually improved and was able to walk with a cane.

Examination showed GEN, which beat leftward, downward, and counterclockwise during the leftward gaze and beat rightward during the rightward gaze. Vertical gaze evoked nystagmus in the direction of gaze. Horizontal smooth pursuit was impaired bilaterally, and saccades were hypometric. Head-bending while sitting induced left-beating nystagmus with a latency of 5 seconds, which, on lying down, converted to prominent right-beating nystagmus with associated vertigo lasting up to 8 minutes. Quick head rotation to either side through 90° while supine induced direction-changing apogeotropic nystagmus (Supplemental video 1, Supplemental Digital Content 1; http://links.lww.com/WNO/A21). (Moving from sitting to supine position immediately induces prominent right-beating nystagmus that lasts for more than 5 minutes. Quick head rotation to either side through 90° while supine evokes direction-changing apogeotropic nystagmus, more marked during left head turning. Head-bending while sitting generates left-beating nystagmus with a latency of 5 seconds. The nystagmus was recorded with the elimination of fixation but could be observed even with fixation.) The positional nystagmus could be observed with fixation, but increased with the elimination of fixation. On neurological testing, the patient had mild bilateral facial diplegia, dysarthria, right arm weakness, head titubation, dysmetria, dysdiadochokinesia, and ataxic gait.

CSF examination and brain MRI were normal. Anti-GD1 IgG antibody was increased (37.5 EU/mL, normal range: <20 EU/mL) while the titer for anti-GQ1b and anti-GM1 antibodies were within normal range. NCS performed 70 days in her clinical course was normal. The patient improved without specific treatment and showed only subtle dysmetria without vertigo or positional nystagmus 4 months after the onset of symptoms.

Case 2

A 16-year-old student presented with vertigo and imbalance for 2 weeks. Initially, he showed downbeat nystagmus and PAN along with horizontal GEN. The PAN reversed its direction every few seconds with a transition period of 1–2 seconds (Fig. 1; Supplemental video 2, Supplemental Digital Content 2; http://links.lww.com/WNO/A22). (The video shows horizontal-downbeat nystagmus. The horizontal nystagmus reverses its direction every few seconds with a minimal transition period [PAN] while downbeat nystagmus persists. The nystagmus was detectable only after...
eliminating fixation and magnifying the eyes using binocular video goggles.) The downbeat nystagmus and PAN were detectable only after eliminating fixation and magnifying the eyes using video goggles. Saccades were hypometric, and smooth pursuit was impaired in both horizontal and vertical directions. The patient had gait ataxia without limb dysmetria. IgG antibody to GQ1b was elevated in the serum at 73.5% (normal range: <20%). Although he showed positive IgM antibody titer in serum for viral capsid antigen of Epstein-Barr virus (EBV-VCA), polymerase chain reaction for EBV was negative. CSF examination, NCS, and brain MRI were normal.

One week later, the patient had positional nystagmus detected with video goggles only with removal of fixation. The nystagmus was geotropic during head turning to either side while supine and during Dix–Hallpike maneuvers. Two months later, PAN and GEN disappeared with improvement of vertigo and imbalance. Subtle right-beating nystagmus developed with the elimination of fixation using left head turn in the supine position, and subtle upbeat nystagmus occurred during left Dix–Hallpike maneuver. Seven months after the symptom onset, the patient reported only mild dizziness with video goggles and showed spontaneous upbeat nystagmus with a slow-phase velocity (SPV) of 6.0°/s, which converted into downbeat nystagmus (SPV at 6.2°/s) with head bending. One year later, the neuro-ophthalmic examination was normal, and the patient denied dizziness or imbalance.

Case 3

A 29-year-old man complained of dizziness and imbalance for 2 months. Initially, he was diagnosed with BPPV involving the right horizontal canal and received a canalith repositioning maneuver. At that time, he had right-beating nystagmus on rightward head turning while supine. One month later, the patient no longer had positional nystagmus.

Two months after developing symptoms, examination with video goggles demonstrated upbeat nystagmus induced by lying down and Dix–Hallpike maneuvers when the fixation was eliminated. The patient showed impaired smooth pursuit and leftward falling on enhanced Romberg test. Elevation levels of anti-GD1b (84.4 EU/mL, normal range: <20 EU/mL) and anti-GM1 (53.8 EU/mL, normal range: <20 EU/mL) IgG antibodies were found in the serum. One month later, patient reported resolution of dizziness and imbalance, and his examination showed no evidence of spontaneous or positional nystagmus.

DISCUSSION

Our patients presented with vertigo, ataxia, and various forms of nystagmus, including vertical, PAN, GEN, and positional nystagmus. The most striking immunological finding was the presence of serum antibodies to GD1b, GM1, or GQ1b. Anti-GD1b antibodies are commonly associated with the ataxic form of GBS (18,22,23). Our patients showed anti-GD1b or anti-GM1 antibodies without features of this disorder. The association of ataxia and nystagmus with these antibodies is supported by the finding that GD1b is present in the cerebellar granular area, dentate and olivary nuclei, sensory ganglia, and spinocerebellar Ia fibers of the peripheral nerves (1,18). A previous study demonstrated that IgM M-protein from a patient with motor neuron disease had antibody activity against the gangliosides GM1, GD1b, and asialo-GM1 (24). In that report, the cerebellar granular cells and white matter were stained with patient’s monoclonal IgM using immunohistochemical methods. These findings support the specific localization of gangliosides GM1 and GD1b both in the granular layer and in the white matter of the cerebellum (24,25).

In our patients, involvement of the cerebellum is likely given the clinical findings of ataxia and various forms of nystagmus, including vertical nystagmus, PAN, GEN, and CPN (26,27). Acute or subacute cerebellar ataxia has been reported in patients with antiganglioside antibodies (13,14,19,22,23). It is unknown if the antiganglioside antibodies are pathogenic, protective, or reactive bystanders.

In general, ataxia associated with antiganglioside antibody has a favorable prognosis. Acquired PAN has been reported in association with a number of conditions (26–28), many of which involve the cerebellum. We could not find previous reports of an association between PAN and antiganglioside antibody. GEN is indicative of inadequate neural integrator function and may be observed in disorders of the brainstem and cerebellum. This includes acute inflammatory autoimmune disorder of the central nervous system, such as Fisher syndrome (21). CPN is usually due to lesions in the caudal brainstem or vestibulocerebellum (27,29). CPN may have various patterns, including direction-changing nystagmus. Two of our patients (Cases 1 and 3) initially were diagnosed with BPPV involving the horizontal semicircular canal. This also may generate direction-changing nystagmus depending on head position (30). However, the associated cerebellar signs and failure to improve with repeated canalith repositioning maneuvers helped establish the central localization (31).

One patient (Case 2) had elevated IgM antibody for EBV-VCA, indicating a recent infection (32). The clinical spectrum of EBV infection includes meningitis, meningoencephalitis, and various neuromuscular complications (33). Possibly, this viral infection in our patient triggered an immune response generating antiganglioside antibodies.

In our patients, the nystagmus was primarily detected when fixation was eliminated using video goggles. This may explain why nystagmus has rarely been reported in association with antiganglioside antibodies (18). For complete evaluation of nystagmus, patients should be examined in various head and eye positions both with and without fixation and with binocular (magnifying) goggles, if available.


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REFERENCES


Protective Effect of Bax Ablation Against Cell Loss in the Retinal Ganglion Layer Induced by Optic Nerve Crush in Transgenic Mice

Nitza Goldenberg-Cohen, MD, Olga Dratviman-Storobinsky, MSc, Shimrit Dadon Bar El, MSc, Yelena Cheporko, MD, Edith Hochhauser, PhD

Background: Bax expression is a prerequisite for retinal ganglion cell (RGC) apoptosis. Experimental studies have reported Bax protein upregulation following optic nerve transection. The stimuli that trigger apoptosis share a common executioner proteolysis cascade, including caspase-3 and poly-(adenosine diphosphate ribose) polymerase cleavage. This study sought to elucidate the role of the mitochondrial apoptotic pathway in RGCs using a Bax transgenic knockout mouse model.

Methods: The right optic nerves of 26 C57BL mice, 7 Bax+/−, 7 Bax−/−, and 12 Bax+/+, were subjected to crush injury and analyzed for apoptosis and neuronal cell loss on days 1, 3, and 21. Levels of Bax, Bcl-2, and caspase-3 messenger RNA expression were determined with real-time polymerase chain reaction.

Results: Multiple apoptotic cells were detected in the retinas of the Bax+/− and Bax−/− mice at days 1 and 3, but not in the Bax+/+ mice. The Bax/Bcl-2 ratio was higher in the Bax+/− than in the Bax−/− mice on day 1 (1.33 and 0.83, respectively), with a trend toward an increase on day 3 (1.47 and 1.66, respectively); Bax/Bcl-X showed the same elevation on day 1 in the wild-type mice (1.34) but decreased on day 3 (0.8). Bax gene expression was undetectable in the Bax−/− mice. Caspase-3 gene expression was higher in the Bax+/− than in the Bax−/− mice on day 1 and dropped toward baseline on day 3. The opposite trend was noted in the Bax−/− mice.

Conclusion: The lack of apoptosis combined with the reduction in proapoptotic genes in the Bax−/− mice after injury compared to the Bax+/+ and Bax+/− mice suggests that Bax plays a crucial role in the induction of apoptosis. Suppression of Bax expression may reduce retinal cell loss.

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RGC apoptosis (5). Bax deficiency protected RGCs after axonal injury by optic nerve crush (6).

The specific molecular pathways involved in transient ischemia-induced apoptosis in the retina are still unclear. Early in vitro studies found that various stimuli that trigger the apoptotic process in retinal cells share a common executioner proteolytic cascade that includes caspase-3 and poly-(adenosine diphosphate ribose) polymerase cleavage. Furthermore, regardless of the stimulus, Bax expression increased during apoptosis, whereas Bcl-2 expression decreased. Treatment with caspase inhibitors blocked the apoptotic cell death (7).

More recent in vitro and in vivo studies demonstrated that purified RGC damage induced by hypoxia involves a Bax-dependent apoptotic pathway (8). A rat model of central artery occlusion was characterized by apoptotic changes in the inner and outer retinal cell layers (9). Using Western blot analysis, the authors found that mitochondrial translocation of Bax from the cytoplasm started at 3 hours and peaked at 6 hours after damage induction. The translocation was accompanied by cytosolic accumulation of cytochrome C and cleavage of caspase-9.

Previous studies evaluated the expression of Bax, Bcl-2, Bcl-X, and caspase-3 genes in the rat retina (9,10). The murine optic nerve crush model simulates the clinical features of traumatic-ischemic damage to the retina. Prompted by our earlier findings that apoptosis is involved in RGC death (11), we sought to elucidate the role of the mitochondrial apoptotic pathway using a Bax transgenic knockout mouse model. Better understanding of ischemia-induced retinal apoptosis may have implications for the development of antiapoptosis agents targeted at the mitochondrial pathway for the treatment of retinal ischemic diseases.

METHODS

Experimental Animals

All protocols were conducted in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and were approved and monitored by the Animal Care Committee of Rabin Medical Center. The animals were housed under a 14-hour light/10-hour dark cycle with standard chow and water ad libitum.

Seven C57BL/6J Bax<sup>−/−</sup> (Bax<sup>tm1Sjk</sup> knockout) congenic mice, 7 C57BL Bax<sup>+/−</sup> (heterozygous) mice (inbred), and 12 C57BL/6 Bax<sup>+/+</sup> (wild-type) mice (from the colony) aged 10 to 12 weeks were kindly provided by Professor Daniel Offen (Neuroscience Laboratory, Felsenstein Medical Research Center, Petah Tiqwa, Israel) (Table 1). Mice genotype was determined by polymerase chain reaction (PCR) as previously described (12), using the following primers: Bax in, GTT GAC CAG AGT GCC GTA GG; Bax ex, TGA TCA GAA CCA TCA TG; and Neo rev, CCG CTT CCA TTG CTC AGC GG.

TABLE 1. Number of mice used for the histological and molecular analyses

<table>
<thead>
<tr>
<th></th>
<th>Bax&lt;sup&gt;−/−&lt;/sup&gt;</th>
<th>Bax&lt;sup&gt;+/−&lt;/sup&gt;</th>
<th>Bax&lt;sup&gt;+/+&lt;/sup&gt;</th>
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<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>H&amp;E (day 21)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Molecular analysis (days 1 and 3)</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td>26</td>
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</tbody>
</table>

H&E, hematoxylin and eosin staining.

Induction of Crush Injury

All 26 mice used in the study were anesthetized with ketamine (80 mg/kg)/xylazine (4 mg/kg) supplemented with topical anesthesia (0.5% proparacaine hydrochloride). Optic nerve crush was performed as previously described (11). In brief, the right optic nerve was crushed by applying forceps at 2.5 to 3.0 mm posterior to the globe for 7 seconds; this procedure was performed 3 times. The left (untreated) eye served as a control. Subsets of mice in each group were euthanized at days 1, 3, and 21 after injury (Table 1); the last time point was selected on the basis of findings that maximal RGC loss occurs 21 days after injury induction (11,13). Paraffin sections of the eyes were analyzed by light microscopy.

Histological Examination

Seven mice were used for histological analysis on day 21 after injury induction. Following euthanization, both the eyes were enucleated and embedded in paraffin, and 5-μm-thick sagittal sections were stained with hematoxylin and eosin and examined under a light microscope. Total retinal thickness was measured at various fields of each section (3 sections in a slide), in a total of 5 to 8 slides. Measurements were performed in triplicate at 180-mm intervals, from the internal to the external limiting membrane. The mean number of cells in the retinal ganglion layer was calculated in a ×40 magnification field of 3 consecutive sections per slide. Each section was sampled in at least 8 different areas.

Apoptosis Assays

Longitudinal cross-sections (5 μm thick) from the paraffin-embedded eyes of 8 mice euthanized on days 1 and 3 were prepared for in situ TUNEL assay (Roche Diagnostics GmbH, Roche Applied Science, Mannheim, Germany); staining was performed with the fluorescein-tagged apoptosis detection system. Results were analyzed with a fluorescence microscope (Fluoview X; Olympus, Tokyo, Japan) at 580 nm wavelength. The mean number of TUNEL-positive cells per slide was determined in 3 consecutive sections per slide, 1 slide for every 10 sections of 5-μm thickness (total 8 slides per eye), with attention to the internal retinal layers. Findings were compared between the...
injured (right) and control (left) eyes of the individual mice and between the injured eyes of the knockout mice and the 2 control groups (Bax+/- and Bax+/-).

Complementary DNA Preparation
Retinal tissues were dissected in a total of 11 mice euthanized on days 1 and 3 after crush injury and snap-frozen in liquid nitrogen. Total RNA was isolated using TRIzol reagent (Invitrogen, Life Technologies, Carlsbad, CA), according to the manufacturer’s protocol, and then reverse transcribed into complementary DNA (cDNA) using random hexamers (Amersham Biosciences, Buckinghamshire, United Kingdom) and Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI).

Apoptosis-Related Gene Expression
Two-stage real-time quantitative polymerase chain reaction (RT-QPCR) was applied to evaluate the expression of Bax, Bcl-2, Bcl-X, and caspase-3 genes after crush injury. The primers list will be provided upon request. Primer efficiency was calculated. We used mouse beta actin (ACTB) to normalize the cDNA input levels because it is known to remain stable under ischemic conditions (14). Analyses were done with the Sequence Detection System (Prism 7000; Applied Biosystems, Foster City, CA). Reactions were performed in a 20-μL volume containing 4 μL of cDNA, 0.5 μM each of the forward and reverse primers, and buffer included in the Master Mix (SYBR Green I; Applied Biosystems). Cycling conditions consisted of an initial denaturation step of 95°C for 10 minutes followed by 50 cycles of 1 minute at 95°C and 1 minute of annealing and extension at 60°C. Triplicate RT-QPCRs were performed for each gene to minimize individual tube variability, and an average was taken at each time point. Threshold cycle efficiency corrections were calculated, and melting curves were obtained using cDNA for each individual gene PCR assay; standard curves were obtained using untreated mouse cDNA for each gene PCR assay. The results were quantified by the comparative threshold cycle (Ct) method (2^-ΔΔCt method) (15), where

\[ \Delta \Delta Ct = \Delta Ct \text{ (sample)} - \Delta Ct \text{ (reference gene)} \]

Statistical Analysis
Group differences in histological and molecular findings were analyzed by Student t test.

RESULTS

Cell Loss in the RGC Layer
Following crush injury, the number of cells in the RGC layer (RGCs and amacrine) decreased significantly in the wild-type and heterozygous Bax mice, by 44% and 23%, respectively (Fig. 1, Table 2). The knockout mice had an increased number of cells in the RGC layer even under normal conditions (left eye) (Fig. 1). After crush injury, the number of cells decreased by 16%, but it was still above the mean of the wild-type mice.

Retinal Thickness
Retinal thickness in the wild-type mice remained constant in the left control eye (mean ± SD, 219 ± 36 μm; range, 206–225 μm; 17% thinning) at 21 days after injury but decreased significantly in the treated eye (mean ± SD, 182 ± 30 μm; range, 175–200 μm; P < 0.05). There was only a mild change in retinal thickness after injury in the Bax-knockout mice (mean ± SD, 329 ± 30 μm vs 338 ± 31 μm of the left control eye; range, 3%), and the final value was significantly higher for the treated wild-type mice (P < 0.05). The retinas of the heterozygous mice were thicker than those of the wild-type mice, measuring 333 ± 34 μm in the left eye (range, 284–369 μm) and 299 ± 31 μm in the right eye (range, 247–384 μm; 11% postinjury thinning).

Cell Apoptosis
Maximal apoptosis of the cells in the retinal ganglion layer was detected on days 1 or 3 after injury in the heterozygous mice (12% and 20%, respectively) and the wild-type mice (15% and 35%, respectively). In the transgenic knockout mice, no apoptotic cells were detected at these time points (Fig. 2, Table 2).

Apoptotic Gene Expression
Bax expression in the wild-type mice was elevated on day 1 and returned to baseline on day 3; in the heterozygous mice, it remained low on days 1 and 3; in the knockout mice, it was undetectable (Table 3). Levels of Bcl-2 and Bcl-X expression in the wild-type mice were elevated on day 1 and then returned to baseline (Bcl-X) or below (Bcl-2). In the heterozygous mice, Bcl-2 levels were below baseline, like the Bax levels. The Bax/Bcl-2 ratio was higher in the wild-type group than that in the heterozygous group on day 1, with a trend for an increase in both the groups on day 3. The Bax/Bcl-X ratio increased on day 1, but decreased to 0.8 on day 3. Caspase-3 expression was higher on day 1 in the wild-type group than in the heterozygous group and decreased toward baseline on day 3. The knockout mice showed an opposite trend, with a decrease in caspase-3 to below baseline on day 1 and its return toward baseline thereafter.

DISCUSSION
Optic nerve crush damage leads to retinal cell death. Apoptosis is known to play a key role in cell death after retinal ischemia. Apoptosis has been described in various models of ischemic ocular injuries, including crush (10,11), glaucoma (6), retinal ischemia (9,16), ischemic optic neuropathy
(13,17), and photoreceptor light damage (18). Studies in transgenic animals suggest that the mitochondrion-mediated apoptosis pathway is involved in ischemia-related cell death. This pathway is triggered by activation of proapoptotic members of the Bcl-2 family of genes (2,10). Accordingly, Bcl-2, Bax, and Bcl-X, as well as activated caspases, may be necessary players in the control of programmed cell death in the RGC layer (19). Studies have reported an upregulation of Bax in RGCs after injury (5); increased survival of injured RGCs when Bax or caspase-3 was inhibited (19); and prevention of RGC death by ablation of the Bax protein (19). In line with these findings, the present study showed that survival of retinal cells of the inner retina, especially in the RGC layer, is increased in Bax-knockout mice subjected to crush injury compared to wild-type and heterozygous Bax mice and that Bax ablation protects the RGCs from apoptosis.

It has been proposed that the ratio of Bcl-2 to Bax or other members of the Bcl-2 family may govern the sensitivity of cells to apoptotic stimuli. Therefore, we investigated the relationship of the Bax (apoptosis promotor)/Bcl-2 (apoptosis inhibitor) ratio and the Bax/Bcl-X (apoptosis inhibitor) ratio and compared the findings with TUNEL staining for apoptosis. On day 1, both the Bax/Bcl-2 and Bax/Bcl-X ratios were upregulated. On day 3, the Bax/Bcl-2 ratio remained high, but the Bax/Bcl-X returned to baseline, in agreement with our histological finding of cell preservation. This suggests that the level of Bcl-X may better reflect the apoptosis state of the RGC layer than the level of Bcl-2 (10). It is of note that we did not find significant changes in these ratios. In a previous ischemia study (20), the Bax/Bcl-2 and Bax/Bcl-X ratios were not modified early after injury, but both were downregulated in the recovery phase, 24 hours later.
TABLE 2. Histological changes in the retina after crush injury

<table>
<thead>
<tr>
<th>Group</th>
<th>Cell Count in the RGC Layer, 21 Days, Mean (±SD) (n = 7)</th>
<th>Cell Loss in the RGC Layer (%)</th>
<th>Retinal Thickness, Mean (±SD) (n = 7)</th>
<th>Apoptotic Cells, % (n/RGC in Field) (n = 8)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crush (RE)</td>
<td>Control (LE)</td>
<td>Crush (RE)</td>
<td>Control (LE)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>14.42* (±2.53)</td>
<td>25.77* (±2.36)</td>
<td>44.0 (±11.32)</td>
<td>252 (±24)</td>
</tr>
<tr>
<td>Bax&lt;sup&gt;+/−&lt;/sup&gt;</td>
<td>25.96 (±0.29)</td>
<td>34.03 (±0.96)</td>
<td>25.6 (±1.83)</td>
<td>299 (±31)</td>
</tr>
<tr>
<td>Bax&lt;sup&gt;−/−&lt;/sup&gt;†</td>
<td>32.35* (±4.46)</td>
<td>38.45 (±2.85)</td>
<td>15.9 (±2.50)</td>
<td>329 (±30)</td>
</tr>
</tbody>
</table>

Retinal sections analyzed for apoptosis were from the central retina: 50 μm diameter around the optic nerve.

*P < 0.05, when comparing cell loss between crush and control of the wild-type and also when comparing crush of Bax<sup>−/−</sup> to wild-type mice.

†The number of RGCs in the Bax<sup>−/−</sup> mice is increased. No apoptosis was detected by TUNEL staining on days 1 and 3. On day 21, there was a 15.9% cell loss in the RGC layer, yet the number of cells remained significantly higher than that in Bax<sup>−/−</sup> mice. Only in the Bax<sup>+/−</sup> mice was retinal thinning detected. No change in the retinal thickness was detected in the Bax<sup>−/−</sup> mice. LE, left eye; RE, right eye.

In our study, RT-QPCR analysis performed 1 day after injury revealed an upregulation of capase-3 expression in the wild-type group. At 1 day after injury, there was a decrease in the level of expression between Bax<sup>+/−</sup> and Bax<sup>−/−</sup> mice and other cell types of the retina. Bcl-X serve as the major antipoptotic gene (10), being at least 16-fold more abundant than Bcl-2. Although we did not measure protein levels, the mRNA expression decreased was noted in Bax, Bcl, and Bcl-X messenger RNA (mRNA) expression. Although we did not measure protein levels, the mRNA expression decreased was noted in Bax, Bcl, and Bcl-X messenger RNA (mRNA) expression.
Thus, staining may give the appearance of an increase in expression because of the aggregation phenomenon. Since the report of Isenmann et al (4), there has been at least 1 independent study describing an increase in Bax mRNA expression in the axotomy paradigm (23) and 2 studies that failed to detect any significant increase (24,25). In the present study, Bax mRNA levels were increased in the wild-type group as early as 1 day after injury.

Semaan et al (24) performed gene dosage experiments in mice, yielding a single wild-type Bax allele. Their findings indicated that genetic background influences the cell death phenotype, including an RGC cell line. This study supports

FIG. 2. Apoptosis assay 1 day and 3 days after crush injury in $\text{Bax}^{-/-}$, $\text{Bax}^{+/+}$, and $\text{Bax}^{+/+}$ mice ($\times 40$). Upper panel: Apoptosis was detected in the RGC layer on day 1 (A–C, TUNEL-positive cells stained in red, arrows) and day 3 (D–F, TUNEL-positive cells stained in red, arrows) in the $\text{Bax}^{+/+}$ (C, F) and $\text{Bax}^{+/+}$ (B, E) mice but not in the $\text{Bax}^{-/-}$ mice (A, D). Lower panel: The graphs summarize apoptosis on day 1 and 3. Wt, wild type ($\text{Bax}^{+/+}$). Control assay (left eye) of $\text{Bax}^{-/-}$ and $\text{Bax}^{+/+}$ mice.
the assumption that quantitative expression of the Bax gene is important in neuronal susceptibility to damaging stimuli. Further support was provided by the elevated Bax mRNA expression in the susceptible species. In the present study, Bax mRNA expression levels were elevated in the wild-type mice at day 1 after crush injury and not in the Bax<sup>−/−</sup> mice. Both the groups, on day 3, showed almost same (baseline) levels of Bax expression.

The decreased apoptosis rate in the inner retina of the transgenic Bax-knockout mice corresponds to observations in a glaucoma model (6) and in ischemic brain (2), liver (26), and heart (12) tissues in other transgenic mouse models. The greater tolerance of the RGCs in the Bax-knockout mice after crush injury also agrees with earlier studies of ischemic ocular injury (20). In wild-type mice in these studies, the number of TUNEL-positive cells reached maximum at 24 to 72 hours after injury (8,11,13,16,17). In contrast, following light damage, Bax<sup>−/−</sup> mice showed no reduction in the number of TUNEL-positive photoreceptor nuclei at 24 hours or 7 days (18). The higher percentage of surviving cells in the RGC layer in our knockout group at 21 days following crush parallels the results reported in the hippocampal region in a transgenic mouse model of neuronal posttraumatic damage (1). Together, these findings support the notion that deletion of the Bax gene ameliorates RGC death after crush injury.

The finding that apoptosis is a significant mechanism of cell death in various eye diseases (ischemia, trauma, or glaucoma, as many other conditions) may have important implications for the development of new treatments that specifically block or interfere with RGC apoptosis. Although this means preventing the result of the disease, not managing its cause, in many patients, ganglion cell death has already been stimulated by the time of diagnosis and continues to progress after conventional treatment.

REFERENCES


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**TABLE 3.** Relative changes in apoptosis-related gene expression after crush injury

<table>
<thead>
<tr>
<th>Group</th>
<th>Apoptosis Gene Expression</th>
<th>Bax</th>
<th>Bcl-2</th>
<th>Bcl-x</th>
<th>Bax/Bcl-2</th>
<th>Bax/Bcl-x</th>
<th>Caspase-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>Day 1</td>
<td>2.05</td>
<td>0.97</td>
<td>0.32</td>
<td>0.64</td>
<td>0.31</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>0.96</td>
<td>0.66</td>
<td>0.32</td>
<td>0.64</td>
<td>0.31</td>
<td>0.66</td>
</tr>
<tr>
<td>Bax&lt;sup&gt;+/−&lt;/sup&gt;</td>
<td>Day 1</td>
<td>0.32</td>
<td>0.32</td>
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<td>0.32</td>
<td>0.32</td>
<td>0.32</td>
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<tr>
<td></td>
<td>Day 3</td>
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Gliomatosis Cerebri Presenting as Idiopathic Intracranial Hypertension in a Child

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Abstract: We present a rare case of a diffuse anaplastic astrocytoma (gliomatosis configuration) in a child, which was misdiagnosed as pseudotumor cerebri following initially normal CT of the brain and elevated opening pressure on lumbar puncture with normal cerebrospinal composition.

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An 11-year-old previously healthy boy was admitted to hospital with headaches and diplopia. Physical and neurological examinations were normal except for bilateral papilledema and right sixth nerve palsy. Brain CT (Fig. 1) and CT venography were normal. The patient underwent lumbar puncture with an opening pressure of 500 mmH₂O, with normal protein and glucose levels, and no cells. Felt to
have idiopathic intracranial hypertension (IIH), he was treated with acetazolamide.

Although the patient reported some improvement in headache, papilledema persisted, and 1 month later, MRI of the brain was performed. This study revealed subtle non-specific signal changes in the right temporal and parietal lobes (Fig. 2). Magnetic resonance venography showed no evidence of venous sinus thrombosis. Another lumbar puncture revealed an opening pressure of 350 mm Hg, with normal cerebrospinal fluid (CSF) content.

Three months later, a second MRI demonstrated diffuse multifocal areas of T2 signal abnormality in the right parietal subcortical white matter and in the right temporal and occipital lobes involving the corpus callosum. These lesions did not enhance following contrast administration.

Five months after initial presentation, a third MRI (Fig. 3) showed progression of the subcortical infiltrative lesions in addition to involvement of the brainstem and superior cervical cord.

FIG. 2. Axial MRI of brain with FLAIR sequences 1 month after initial presentation. A. There is an increased signal and slight enlargement of the right temporal lobe (arrows). B. More rostrally, there are subtle signal abnormalities (arrows) in the right parietal lobe without mass effect.

FIG. 3. Axial FLAIR MRI of the brain 5 months after initial presentation. A. Subcortical signal changes in the right temporal lobe (arrow) with effacement of the sulci. B. Enlargement of the lesion in the right parietal lobe (arrow).
The patient underwent an open brain biopsy (Fig. 4) revealing anaplastic cells, which were positive for glial fibrillary acidic protein, and the proliferation marker MIB1 was present in 15%–20% of the cells (World Health Organization grade 3). Necrosis and vascular proliferation were absent. These findings were compatible with anaplastic astrocytoma, and the treatment with whole brain irradiation was initiated.

A number of neoplastic disorders of the central nervous system can mimic IIH. One such example is nonsolid tumor infiltration of the leptomeninges. While this disorder may cause only subtle changes on neuroimaging (1–3), there is often a CSF pleocytosis with elevation in protein. Spinal cord tumors may also mimic IIH but are likely to be evident in imaging (1). The most challenging masquerading lesion is an infiltrative brain tumor that does not cause mass effect, nor influence CSF composition, and may not be detected on initial neuroimaging (1,4). As our case illustrates, this may occur in gliomatosis cerebri (5).

Armstrong et al (6) reported a cohort of 13 pediatric patients with gliomatosis cerebri. The median age at time of diagnosis was 12 years, and 77% of patients were male. The most common presentation was seizure followed by hemiparesis. Only 1 patient reported headache. Frequency of papilledema was not stated, although on neuroimaging 8 patients demonstrated mass effect and 2 had hydrocephalus. Vates et al (7) described 22 patients with gliomatosis cerebri with only 1 in the pediatric age-group (6 years). Papilledema was present in 27% of cases, and in all these patients, there were varying degrees of mass effects on MRI. In contrast, our patient had papilledema without evidence of mass effect on initial neuroimaging. There are few reports of gliomas mimicking IIH. Weston and Lear (5) reported the case of a 44-year-old woman with signs of increased intracranial pressure, including papilledema. Initial brain CT and CSF analysis were normal. Despite undergoing a CSF shunt procedure, the patient continued to deteriorate, and 7 months later, brain MRI showed an infiltrating tumor of the cerebral hemisphere (5) and brain stem. Stereotactic biopsy confirmed the diagnosis of gliomatosis cerebri. Aroichane et al (8) documented the case of a 16-year-old girl on minocycline who presented with headaches for 12 months and diplopia and papilledema for 5 weeks. Brain MRI and CSF were normal, although the authors state that some neuroradiologists felt that there was subtle non-enhancing enlargement of the thalami, optic chiasm, and infundibulum. Eight weeks later, vision declined in the left eye, there was an incomplete bitemporal hemianopia on perimetry, and MRI now revealed a large mass involving the optic chiasm and diencephalon. This proved to be a glioblastoma multiforme.

Similarly, our case serves to emphasize that IIH is a diagnosis of exclusion, and patients must be monitored carefully. After initiating treatment, if neuro-ophthalmic signs and symptoms persist or progress, repeat neuroimaging is mandatory. Even subtle and seemingly non-specific findings on imaging studies must be closely monitored.

REFERENCES

Postinfectious Optic Neuropathy in Endemic Typhus

Jason Zhang, BA, Derrick Pau, MD, Andrew G. Lee, MD

Abstract: Endemic typhus (Rickettsia typhi), also known as murine typhus, is a flea-borne bacterial disease rarely found in most of the developed world. Known ocular manifestations linked to endemic typhus include mild vitritis, retinal lesions, and retinal vascular leakage. Optic neuropathy, however, is rarely associated with R. typhi, and postinfectious optic neuropathy is even less common. To highlight this unusual complication, we report a patient who developed postinfectious optic neuropathy a few weeks after he was successfully treated for endemic typhus.

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Endemic typhus (Rickettsia typhi), also known as murine typhus, is a flea-borne bacterial disease rarely found in most of the developed world (1). Known ocular manifestations linked to endemic typhus include vitritis, retinal lesions, and retinal vascular leakage (2–4). Optic neuropathy is rarely associated with R. typhi, and postinfectious optic neuropathy is even less common. To highlight this unusual complication, we report a patient who developed postinfectious optic neuropathy a few weeks after he was successfully treated for endemic typhus.

A 63-year-old white man was hospitalized 2 months prior to his visual symptoms for serologically confirmed endemic typhus (Rickettsia typhi). During that hospitalization, he had high fever, a diffuse maculopapular rash, and delirium. He subsequently developed hepatic and renal failure, meningoencephalitis, and pancytopenia secondary to hemophagocytosis. Extensive testing for infectious, inflammatory, and infiltrative etiologies was negative except for \( R. typhi \) titers for IgM (1:8192) and IgG (1:256). The patient received a 2-week regimen of doxycycline and was discharged after he completely recovered from his multiorgan failure, with a return to baseline of his laboratory abnormalities. Three weeks later, the patient presented to the emergency room with acute painless visual loss in the right eye. He had no other significant medical history.

On neuro-ophthalmic examination, the patient was afebrile, with visual acuity of 20/800, right eye, and 20/25, left eye. There was a right relative afferent pupillary defect (RAPD). Slit-lamp biomicroscopy showed no anterior uveitis. Extracocular movements, external examination, and intraocular pressures were normal. Ophthalmoscopy revealed mild vitritis and optic disc edema in the right eye (Fig. 1) while the left fundus was normal. The left optic disc had a cup-to-disc ratio of 0.3. Automated visual fields (10-2) showed a central scotoma and the mean deviation (MD) of –11.38 dB on the right eye while the left visual field was normal. Fluorescein angiography showed mild right optic disc leakage.

Repeat serological testing for \( R. typhi \) showed an IgM titer of 1:256 and IgG titer of 1:512. MRI of the brain and orbits showed no optic nerve or meningeal enhancement. Cerebrospinal fluid analysis was unremarkable. The patient was treated with systemic doxycycline and a tapering course of intravenous corticosteroids. Three months later, his visual acuity was 20/200 in the right eye. The right optic disc was pale (Fig. 2), and optical coherence tomography of the right eye showed decreased peripapillary retinal nerve fiber layer thickness of 70 \( \mu \)m (normal: 100 ± 10 \( \mu \)m). Repeat right visual field testing (automated 24-2) demonstrated an MD of –0.74 dB, with reduction in the size and density of the central scotoma.

The ocular manifestations of endemic typhus previously have been described, and retinal abnormalities predominate (2–4). In a prospective study of 9 patients (2), the most common ocular findings were vitritis (55.6%), white retinal lesions (50%), and retinal vascular leakage (38.9%). Symptoms were largely bilateral and often accompanied by choroidal involvement. One patient presented with left optic neuritis associated with a sudden decrease in vision...
to 20/40, a left RAPD, and a swollen optic disc. Over an 8-week period, vision improved to 20/25 and the left disc became pale. While the patient was asymptomatic in the right eye, white retinal lesions and retinal vascular leakage were noted in that eye.

While previous reports mainly documented rickettsia-associated ocular manifestations in the context of active infection, our patient is unusual in that his visual symptoms developed weeks after recovery from the acute illness. He presented with mild vitritis without evidence of chorioretinal abnormalities. The absence of these findings suggests a different pathogenesis in the postinfectious state or possibly these fundus abnormalities had resolved by the time of examination. Our case is also atypical in the severity of the vision loss. In previous endemic typhus cases, ocular changes were mostly asymptomatic (2–4). In the report by Khairallah et al (2), only 3 of 9 patients had ocular complaints with visual acuity ranging from 20/20 to 20/40.

The exact mechanism of endemic typhus–associated optic neuropathy is unknown but is likely on an immune basis. It has been speculated that retinal manifestations arise from rickettsia-induced deposition of intraretinal immune complexes and inflammatory cells (2). Repeat serological tests in our patient were positive for R. typhi, and falling convalescent IgM titers make recrudescent typhus (Brill-Zinsser disease) unlikely. In addition, the timing of visual loss in our patient supports an immunological mechanism. Treatment of postinfectious optic neuropathy with high-dose corticosteroids appears reasonable but should be avoided during active infection.

The possibility of nonarteritic anterior ischemic optic neuropathy was considered in our patient. However, the close temporal relationship between the systemic illness and the optic neuropathy, the absence of vasculopathic risk factors (e.g., diabetes, hypertension, elevated cholesterol), and the absence of a “disc at risk” in the fellow eye made this diagnosis unlikely.

REFERENCES

Subacute Bilateral Visual Loss in Methylmalonic Acidemia

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Abstract: A 23-year-old woman known to have methylmalonic acidemia (MMA) since birth suffered bilateral visual loss over 5 days. Her disease was well controlled by strict diet and carnitine supplementation. Multiple sclerosis, Leber hereditary optic neuropathy (LHON), and infectious, nutritional, and vasculitic causes were ruled out. MRI showed enhancement of both optic nerves. Toxic damage of both optic nerves due to MMA was the most likely mechanism. Treatment with high-dose intravenous corticosteroids and coenzyme Q10 combined with vitamin E was ineffective. Although optic nerve involvement previously has been reported in MMA, the neuroimaging findings in our case make it unique. MMA is a rare metabolic disease of autosomal recessive inheritance resulting in mitochondrial dysfunction. Affected patients commonly present in the neonatal period or in early infancy with a severe metabolic encephalopathy, metabolic acidosis, failure to thrive, developmental delay, various neurological symptoms, and eventually multiorgan dysfunction (1). The disorder is caused by deficient activity of the enzyme methylmalonyl-CoA-mutase or by defects of intracellular synthesis of its cofactor adenosylcobalamin (coenzyme form of vitamin B12). The deficiencies caused by mutations in the apomutase locus are further subdivided into defects without activity (mut0) and defects with residual activity (mut+). Impaired degradation of the amino acids (valine, isoleucine, methionine, and threonine), of odd-chain fatty acids and cholesterol side chains, and of thymine and uracil results in an accumulation of methylmalonic acid and other toxic metabolites. This is thought to cause secondary mitochondrial dysfunction (2).

Preclinical studies and tissue analyses from patients with MMA suggest that mitochondrial impairment occurs through a combination of inhibition of specific enzymes and transporters, limitation in the availability of substrates for mitochondrial pathways, and oxidative damage (3). Disruption of mitochondrial homeostasis may lead to impairment of energy metabolism and further increase in reactive oxygen species due to reduced electron flow in the mitochondrial respiratory chain (4). Therapy is mainly based on a diet low in propionic amino acids and high in energy (1).

There have been reports of optic atrophy associated with organic acidurias in early childhood (5,6). Late-onset optic neuropathies in adolescence or adulthood associated with MMA have been reported by 2 groups with ages ranging from 15 to 21 years (7,8). In our patient, optic neuropathy developed later but more rapidly and showed a morphological correlate on MRI.

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The authors report no conflicts of interest.

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CASE REPORT

Our patient is a 23-year-old woman with MMA who 4 days after birth developed generalized hypotonia, hypothermia, and dyspnea. Diagnosis of MMA was confirmed by severely decreased methylmalonyl-CoA-mutase activity in cultured fibroblasts and later by compound heterozygosity for p.A137V/p.N219Y in the MUT gene, compatible with a mutante defect (Patient 006 in Lempp et al, 2007 [9]). She had a mild developmental delay, impaired renal function, a hypothalamo-hypophyseal insufficiency with growth retardation, and a history of abnormal puberty.

The patient experienced bilateral visual loss with rapid deterioration over 5 days. Initial neuro-ophthalmic examination 5 days after the onset of symptoms revealed finger counting vision in each eye with large pupils that reacted poorly to light; slight, bilateral, posterior subcapsular cataracts; cecocentral scotomas on kinetic perimetry, and normal fundi. The neurological examination was otherwise normal. An electroencephalogram was normal, and visual evoked potentials showed prolonged latency of the P100 component bilaterally.

MRI performed 2 weeks later showed enhancement of both optic nerves (Fig. 1) and symmetric T2-hyperintense lesions in the posterior limb of each internal capsule.

Given the possibility of an inflammatory optic neuropathy, high-dose intravenous steroid therapy was administered for 5 days without improvement. Testing for LHON, vasculitis, infections, including syphilis, and vitamin B1, B6, B12, and folic acid deficiency was all normal. Cerebrospinal fluid analysis was unremarkable. MRI of the spine and neuromyelitis optica antibody testing were not performed. Supplementation with coenzyme Q10 (180 mg/d) combined with vitamin E (200 mg/d) started 7 months after onset of symptoms failed to improve visual function.

Three months after the onset of vision loss, the patient developed subacute partial neurosensory hearing loss. At 6 months, she experienced a further decline in vision to hand motions in each eye and the optic discs were found to be diffusely pale. At 9 months, vision remained unchanged and the patient remained metabolically well controlled, adhering to a therapeutic diet and carnitine supplementation.

DISCUSSION

Ophthalmologic findings in MMA infrequently have been reported. Cataract formation has been described by Stromme et al (10) in 2 siblings with atypical MMA. De Baulny et al (5) mentioned 2 patients who developed optic atrophy and neurosensorial deafness but did not provide clinical details. Severe optic neuropathy in MMA has been reported in 3 patients. Williams et al (8) described 2 men with vision loss over 3–4 weeks: a 16-year-old with acuity of 20/300, right eye, and 20/150, left eye, and a 21-year-old with acuity of 20/200 in each eye. Pinar-Sueiro et al (7) reported a 15-year-old girl with vision loss to 20/400, right eye, and 20/40, left eye, occurring over 5 weeks. These patients underwent either CT or MRI without detection of optic nerve abnormalities.

We postulate that the underlying cause for bilateral optic neuropathy and neurosensorial hearing loss in our patient is due to a delayed progressive breakdown of mitochondrial function with induction of neuronal cell death. This hypothesis (8) is supported by growing evidence of in vitro and in vivo studies suggesting an inhibition of mitochondrial metabolism in MMA (2,3), as well as the similarity to the clinical profile of LHON and other mitochondrial optic neuropathies (11).

The reason for the delayed onset of optic neuropathy in patients with MMA and the closely related condition of propionic acidemia (PA) may be due to the fact that only low amounts of methylmalonic acid (only in MMA) and other dicarboxylic acids (in MMA and PA) are produced in the brain. Since the blood–brain barrier is virtually impermeable to these dicarboxylic acids, they slowly accumulate within the central nervous system and induce delayed mitochondrial dysfunction (2,3). The resulting ATP depletion with collapse of ion gradients may result in Ca++ influx and induction of mitochondrial permeability transition (MPT),

**FIG. 1.** Contrast-enhanced T1 axial (A) and coronal (B) MRI reveals enhancement (arrows) of both optic nerves.
which induces apoptosis (12). Oxidative stress is an important inducer of MPT as well (3,13). With loss of cellular homeostasis and cell death, there is a breakdown of the blood–brain barrier. This may explain the optic nerve enhancement seen on MRI in our patient.

Currently, there is no effective therapy for MMA. Treatment with coenzyme Q10 and vitamin E have been described (7,8). Coenzyme Q10, an essential cofactor in the mitochondrial respiratory chain, has gained attention for its neuroprotective properties and its potential role in the treatment of neurodegenerative (14) and mitochondrial (15) diseases. Its neuroprotective effect is related to antioxidant activity and to a specific regulation of the MPT pore (16,17). Coenzyme Q10 has been shown to be reduced in fibroblasts of patients with MMA (18). Vitamin E is a well-known free radical scavenger (19,20). While Williams et al (8) were unable to show any benefit with the use of coenzyme Q10, Pinar-Sueiro et al (7) reported a significant improvement in visual function after treatment with coenzyme Q10 (200 mg/d) and vitamin E (200 mg/d). However, this treatment regimen was ineffective in our patient.

REFERENCES

Cortical Blindness Following a Near-Drowning Incident

Ellen H. Koo, MD, Jerrold L. Boxerman, MD, PhD, Marjorie A. Murphy, MD

Abstract: Victims of near-drowning incidents often suffer neurologic injury with long-term sequelae secondary to hypoxic-ischemic injury. We describe a case of profound visual loss due to bilateral occipital lobe infarcts in a 23-year-old male victim of a near-drowning incident.

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Near-drowning is a term applied when an individual survives for at least some period after suffocation from submersion in a liquid (1). The primary mechanism of injury is pulmonary failure caused by fluid aspiration, which results in severe arterial hypoxemia and secondary ischemic damage to other organs, including the brain (2). Victims of near-drowning incidents often suffer neurologic injury with long-term sequelae secondary to hypoxic-ischemic injury (3). We describe a case of cortical blindness due to bilateral occipital lobe infarcts following a near-drowning incident.

A 23-year-old man was found unresponsive at the beach after a near-drowning incident while surfing. He was intubated and admitted to the Trauma Intensive Care Unit. CT of the chest showed bilateral airspace disease consistent with aspiration. MRI of the cervical spine showed a fracture of the C-5 vertebral body that did not require surgical intervention.

Shortly after the patient was extubated on the fourth day of his hospitalization, he complained of profound bilateral vision loss. He was awake, alert, and cooperative with the examination. Visual acuity was counting fingers in both eyes, and ophthalmologic examination was otherwise normal. CT of the brain was unremarkable while MRI with FLAIR sequences revealed widespread areas of abnormal hyperintensity (Fig. 1, top panel). Diffusion-weighted images (DWI) confirmed the presence of restricted diffusion in the affected regions (Fig. 1, middle panel), and these changes were consistent with cytotoxic edema (Fig. 1, bottom panel). There was no improvement in vision upon his discharge from the hospital 6 days later. The patient refused further follow-up.

The causes of cortical blindness may be broadly divided into vascular, toxic, traumatic, infectious, and neurodegenerative. Near-drowning leads to severe arterial hypoxemia and secondary ischemic infarcts of the brain (2) and is a potential vascular source of injury leading to cortical blindness.

During a drowning or a near-drowning event, cardiopulmonary failure from aspiration causes decrease in cerebral blood flow leading to ischemic injury (2). The areas of greatest susceptibility to ischemic injury are usually the vascular end zones ("watershed" areas), as well as the hippocampus, insular cortex, and basal ganglia (4). However, with greater severity of hypoxic ischemia, more extensive and global neocortical damage can occur (4).

Posterior reversible encephalopathy syndrome (PRES) is another vascular etiology of cortical blindness (5,6). This seems unlikely in our patient. First, PRES is typically precipitated by sudden hypertension and is associated with headache, seizure, visual disturbance, and altered mental function (6). In cases of near-drowning, the mechanism of injury to the brain is associated with hypotension and hypoxia (7). Second, the lesions of PRES on DWI are usually isointense or hypointense, with areas of increased signal on apparent diffusion coefficient (ADC) maps indicating vasogenic edema (5). In our patient, the results of DWI indicated cytotoxic edema. Third, PRES is usually reversible with a favorable visual outcome while our patient remained severely visually impaired.

Following cold-water submersion, protecting the brain from hypoxic injury can be favorably modified by the coexistence of hypothermia (8). Cold water is considered to be neuroprotective in near-drowning due to cold-induced
decrease in cerebral metabolic rate for oxygen (9,10). In animal studies, brain temperature below 85°F is thought to provide an increased protection against anoxia (11), and this appears to be the case in humans as well (12). The water in which our patient was found ranged in temperature from 68.71°F to 71.89°F. It is possible that this cold-water

FIG. 1. Top panel: Axial FLAIR images demonstrating abnormal hyperintense signal (arrowheads) in the frontoparietal (A) parieto-occipital (B), and temporo-occipital (C) cortex. There is also involvement of the caudate nuclei (arrows) (B). Middle panel: Axial DWI scans reveal bilateral scattered regions of abnormal gyriform signal hyperintensity corresponding to regions of signal abnormality detected on FLAIR images. Bottom panel: In areas of DWI hyperintensity, apparent diffusion coefficient (ADC) maps showing reduced signal consistent with cytotoxic edema.
submersion allowed some degree of neuroprotection, thereby leading to focal infarcts rather than diffuse cerebral involvement.

REFERENCES
Periodic Unilateral Eyelid Retraction in a Pediatric Patient

Nandini G. Gandhi, MD, Gina M. Rogers, MD, Randy H. Kardon, MD, PhD, Richard C. Allen, MD, PhD

Abstract: A healthy 11-year-old girl presented with right upper eyelid retraction since birth. An evaluation including thyroid function studies and neuroimaging was negative, and the patient was scheduled for a right levator recession to address the eyelid malposition. Intraoperatively, after the induction of inhalational general anesthesia, the patient displayed cyclic right upper eyelid retraction. Occurring in intervals of exactly 48 seconds, these cycles involved a rapid elevation of the right eyelid from a position of half-closure to a retracted position just above the superior limbus. There was no change in pupil size or eye position during these cyclic spasms, and the contralateral eyelid was unaffected. The patient underwent an uncomplicated levator recession, which improved the upper eyelid retraction. Postoperative testing, including external motility video and infrared pupillometry, demonstrated no cyclic variation in eyelid position, eye position, or pupil size in the waking state. This is a unique case of unilateral eyelid retraction with periodic spasms under conditions of anesthesia without a pre-existing oculomotor paresis; it represents an unusual variation on congenital eyelid retraction and classically described cyclic oculomotor palsy.

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Congenital eyelid retraction in children has been reported in isolation and in association with disease processes, such as thyroid dysfunction, aberrant innervation of the third nerve, and levator fibrosis (1,2). Cyclic spasms associated with eyelid retraction have been reported almost exclusively in the setting of pre-existing oculomotor paresis and are thought to be the result of aberrant innervation (3–8). We present the case of a child with unilateral eyelid retraction and no pre-existing oculomotor paresis who demonstrated periodic spasms of eyelid retraction after the administration of inhalational anesthesia. We discuss the differential diagnosis and appropriate workup for congenital eyelid retraction and propose possible mechanisms for this patient’s unusual presentation.

CASE REPORT

A healthy 11-year-old girl presented for evaluation and management of right upper eyelid retraction since birth. The patient was the full-term product of an uncomplicated pregnancy and nontraumatic vaginal delivery. The family reported that the right upper eyelid had been retracted since birth, with no noticeable change in the position over time. They also noted that the patient’s eyelids remained closed during sleep without abnormal movement of the eyelid while asleep. There was no history of proptosis, strabismus, or periocular/facial trauma, and she took no medications and had no known medication allergies.

On initial examination, the patient had right upper eyelid retraction without proptosis (Fig. 1A). The palpebral fissure measured 11.5 mm on the right eye and 9 mm on the left eye. The margin reflex distance-1 measured 6 mm on the right eye and 3.5 mm on the left eye. Levator function was normal on each side at 15 mm, and the patient demonstrated right lid lag on downgaze (Fig. 1B). The patient had full ductions and versions, and there was no variation in upper eyelid position, with changes in gaze position. The right lower eyelid elevated slightly on upgaze.
(Fig. 1C), and there was no change in eyelid position with jaw movement. Pupils were isocoric without variation in pupil size in different gaze positions. The anterior and posterior segment examination of both the eyes was normal, with the exception of mild superficial punctate epitheliopathy of the right cornea.

Thyroid function studies and MRI of the brain and orbits were normal. It was assumed that the eyelid retraction was idiopathic and isolated, and the decision was made to proceed with a right levator recession.

After the induction of general anesthesia with inhaled sevoflurane and before the administration of local anesthetic, the patient displayed periodic spasms of right upper eyelid retraction (see Video, Supplemental Digital Content 1, http://links.lww.com/WNO/A23). Occurring in intervals of exactly 48 seconds, these cycles involved a rapid elevation of the right eyelid from a position of half-closure to a retracted position just above the superior limbus. The eyelid slowly drifted down to a position of half-closure after 8 seconds of full retraction. There were no fasciculations, changes in pupil size, or alterations in eye position during these spasms. The left eyelid was unaffected. The patient was observed for a total of 10 minutes, and these cycles occurred in exactly the same time interval. Of note, the patient had not received any other medications in the preceding 24 hours. Given that these spasms were not seen during wakefulness, the decision was made to proceed with surgery.

At the 3.5-month postoperative visit, the right upper eyelid position had improved (Fig. 2). There were no cycles of eyelid retraction detected after prolonged observation in the clinic. Upon questioning, the family denied any changes in eyelid position during wakefulness or during sleep. The patient was videotaped with the eyelid position observed in primary position and in downgaze for 5 minutes each: no cyclic variation of eyelid position was detected. Infrared pupillometry performed for 5 minutes likewise demonstrated no cycles of miosis or mydriasis of either eye. Ocular motility was once again confirmed as being normal.

DISCUSSION

We were unable to find other reports of unilateral eyelid retraction with periodic spasms without a pre-existing oculomotor paresis under conditions of inhalational general anesthesia. This case represents an unusual variation on isolated pediatric upper eyelid retraction and classically described oculomotor palsy with cyclic spasms.

Upper eyelid retraction in children has been reported in isolation and in association with systemic and local disease processes (1,2,9–13). The diagnosis of primary, isolated congenital eyelid retraction can be made only when systemic conditions and neurological injury have been excluded. In a review of 16 pediatric patients with unilateral and bilateral eyelid retraction, Stout and Borchert (1) found that the most common causes were hyperthyroidism (either acquired or congenital), aberrant innervation, and local tissue changes (orbital lesions or fibrosis of the levator complex). Abnormally dense extensions of the lateral and medial horn of the levator at the level of the Whitnall ligament have been documented in cases of isolated congenital eyelid retraction (2). Posttraumatic upper eyelid retraction secondary to adhesions between the levator complex and other orbital structures has also been reported (10).

**FIG. 1.** A. In primary position, the patient demonstrated 2.5 mm of right upper eyelid retraction and is orthophoric. B. In downward gaze, there is right lid lag. C. In upward gaze, there is an elevation of the right lower eyelid.

**FIG. 2.** Postoperative appearance at 3.5 months shows no evidence of right eyelid retraction.
Oculomotor palsy with cyclic spasms is a rare condition first described in 1884 by Rampoldi (8) as “oculo-palpebral imbalance” in a healthy 4-year-old girl. In their review of the literature through 1975, Loewenfeld and Thompson (6) identified only 54 cases; Miller and Lee (7) identified an additional 31 cases between 1975 and 2003. The majority are characterized by the presence of an oculomotor palsy with regular cyclic spasms of varying degrees of eyelid retraction, adduction of the globe, and/or pupillary mydriasis (3–8,14). Loewenfeld and Thompson (6) calculated the average time of each cycle is 73.6 seconds (with a range of 20 seconds to 3.5 minutes), with the paretic phase being consistently longer than the spastic phase in nearly all cases. The exact mechanism of cyclic oculomotor palsy is unknown. Most theories invoke the principle of aberrant innervation following an initial insult to the oculomotor nerve, but the question of whether the process is primarily supranuclear or infranuclear remains controversial (3,6,14,15).

Our case combines features of isolated eyelid retraction and cyclic oculomotor palsy but is distinct from all previously reported cases. First, in spite of the idiosyncratic cyclic spasms of eyelid retraction, our patient had no evidence or history of pre-existing oculomotor paresis. Second, our patient’s eyelid was affected in isolation without involvement of the extraocular muscles or pupillary muscles. Finally, the cycles were only present during inhalational general anesthesia. The mechanism for our patient’s clinical findings is unclear. If we assume a neurological basis, both peripheral and central factors may be involved. The unilaterality of the eyelid spasms speaks to peripheral nerve involvement, whereas the rhythmic cycles that were unmasked with general anesthesia suggest disinhibition of central control. It is possible that the patient had an injury in utero or in the perinatal period that affected some fibers of the superior division of the third nerve. The patient’s eyelid retraction suggests sustained overaction of injured axons that have reinnervated the levator muscle, and the presence of normal levator function is consistent with a population of uninervated the levator muscle, and the presence of normal innervation.

The periodic nature of our patient’s eyelid retraction may be due to development of abnormal supranuclear connections. These connections might transmit impulses that overcome levator inhibitors (6,16). Levator inhibition is unnecessary while awake but is required during general anesthesia.

Alternatively, it is possible that this phenomenon is a pharmacologic effect of inhaled sevoflurane. Sevoflurane has been implicated in causing localized or generalized tonic-clonic movements at the end of induction (17–19). These signs are often accompanied by burst suppression on electroencephalography, indicating altered cortical activity as a possible cause for the seizure-like movements (18). Possibly, our patient’s eyelid retraction was due to myopathic changes in the levator, making it susceptible to the effects of sevoflurane. However, we were unable to find any reports of periodic muscle spasms with the inhalational anesthetics in conditions of generalized myopathy.

Infants and children presenting with unilateral eyelid retraction without an obvious ocular syndrome warrant a careful history and workup to identify an underlying cause. Thyroid function studies should be performed to rule out congenital or acquired thyroid disease. Imaging of the brain and orbits should be performed with special attention to the entire course of the third nerve to rule out a mass lesion, evidence of trauma, or other structural abnormalities. The possibility of cyclic eyelid retraction should be considered, especially in those patients with evidence of a pre-existing oculomotor palsy. Careful observation of these patients in the outpatient setting is advised prior to workup and surgical planning.

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Role of the Macular Optical Coherence Tomography Scan in Neuro-Ophthalmology

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Background: Recent improvements in optical coherence tomographic (OCT) resolution and automated segmentation software have provided a means of relating visual pathway damage to structural changes in the retinal nerve fiber layer (RNFL) and corresponding soma of the ganglion cells in the inner layers of the macula and also in the outer photoreceptor layer in the macula.

Evidence Acquisition: Studies correlating retinal structure with function are reviewed in the context of OCT in optic nerve and retinal disorders.

Results: Recently published work provides evidence showing a strong relationship not only between the RNFL and visual threshold in optic nerve disorders but also between visual sensitivity and the inner layers of the retina in the macula, where the cell bodies of ganglion cells reside. Acquired and genetic disorders affecting the outer retina show correlation between visual sensitivity and the thickness of the outer photoreceptor layer. These relationships help localize unknown causes of visual field loss through segmentation of the retinal layers using spectral domain OCT.

Conclusions: Advances in relating the structure of the ganglion cell layer in the macula to the corresponding axons in the RNFL and to visual function further our ability to differentiate and localize ambiguous causes of vision loss and visual field defects in neuro-ophthalmology. Ganglion cell layer analysis in volume OCT data may provide yet another piece of the puzzle to understanding structure-function relationships and its application to diagnosis and monitoring of optic nerve diseases, while similar structure-function relationships are also being elucidated in the outer retina for photoreceptor diseases.

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Most clinicians, especially neuro-ophthalmologists and glaucoma specialists, have been trying to understand whether the information yielded by optical coherence tomography (OCT) is really helping them to improve upon the clinical care of their patients. Since its inception, OCT had provided new information about the status of the optic nerve, in terms of axon loss, providing information about the thickness of the retinal nerve fiber layer (RNFL). As neuro-ophthalmologists have attempted to incorporate the quantification of RNFL thickness into their decision making, they have gained new insight into both its clinical usefulness and its limitations. Recently, the use of the macular OCT has helped to further expand the usefulness of OCT in neuro-ophthalmology patients, especially as spectral domain optical coherence tomography (SD-OCT) has improved resolution and shortened the time for sampling of tissue volume. More advanced image analysis algorithms have improved the ability to segment the retinal layers in the macula, allowing improved detection and differentiation of the cause of visual loss.

RNFL IN NEURO-OPHTHALMOLOGY: USEFULNESS AND LIMITATIONS

In the past, the use of OCT in neuro-ophthalmologic clinical decision making has primarily focused on the status of the RNFL thickness in relation to the threshold sensitivity of the corresponding area of visual field (1). Theoretically, it is expected that the degree of thinning of the RNFL will have a meaningful correlation with optic nerve function in a patient with loss of axons (2–4) and less correlation of structure with function in locations where axons are still intact but not functioning. In the latter case, either a return of function may still be possible, as in the case with some eyes with compressive optic neuropathy (5), acute optic neuritis (6–9), or ischemic optic neuropathy. Alternatively, the axons may have undergone irreversible dysfunction but not enough time has elapsed to produce atrophy and thinning of the RNFL (1). It has generally been accepted that acquired postgeniculate damage to the visual pathway in
adults usually does not result in trans-synaptic retrograde
degeneration with optic atrophy. Recently, evidence has
been published, which has questioned this by showing thin-
ning of the RNFL in each eye of patients with homony-
mous field loss, corresponding to what would be expected
if trans-synaptic degeneration had taken place (10). Such
results need confirmation with detailed MRI evaluation to
certify that the acquired pathology is restricted to the
postgeniculate visual pathway and does not involve the
optic tract.

The clinical interpretation of axon loss becomes even
more difficult in the setting of optic disc edema associated
with visual field loss, since there may be swelling of some
axons with atrophy of neighboring axons, confounding the
relationship between RNFL thickness and corresponding
visual field sensitivity. This is where evaluation of the
thickness of the retina in the macula or its inner layer
may be helpful, since the RNFL contributes very little to
macular thickness. Loss of neurons in the setting of optic
disc edema would be likely to be detected in the macula,
where the ganglion cell layer would become thinner over
time as atrophy takes place. This situation is most common
in conditions where the optic disc edema lasts more than
a few weeks, such as in anterior ischemic optic neuropathy
(AION), papilledema from raised intracranial pressure,
orbital optic nerve sheath meningioma with associated disc
edema from venous stasis retinopathy, and in some cases of
compressive optic neuropathy in the orbit, as in Graves
orbitopathy.

Another potential confounding variable is the status of
other components that make up the thickness of the RNFL,
besides axons, such as blood vessels and glial elements,
which may influence the measured thickness of the RNFL
(1,11,12).

Attempts to quantify the relationship between structure
and function between RNFL thickness and visual threshold
at corresponding locations have revealed that there is
a correlation (primarily studied in glaucoma and AION)
but not as great as one would expect (1–4). Factors such as
measurement variability in both visual threshold and RNFL
thickness, the influence of nonneuronal elements on the
RNFL thickness, such as blood vessels and glial elements,
and the interindividual variation in mapping of RNFL bun-
dles to their corresponding area of the visual field confound
the correlation in an individual patient. We have recently
reviewed this topic (1) and have provided evidence for a linear
model relating visual threshold (unlogged) and RNFL
thickness in glaucoma and AION (2–4). This is depicted in
Figure 1 in semi-log plots. If the data in Figure 1 were
replotted with both axes on a linear scale, the relationship
would be a straight line. The significance of the linear rela-
tionship provides evidence against a critical tipping point
where loss of structure precedes loss of function. Rather, the
fit of data to a linear model implies they are both propor-
tionate to one another across all levels of disease severity.

While the relationship between RNFL thickness and
visual field sensitivity appears to correspond to a linear
model, there are still components of measurement variabil-
ity (such as the variability between and within subjects) that
impose limitations on this framework and its application to
individual patients (Fig. 2). In addition, the dynamic range
of both the RNFL and visual threshold sensitivity and their
associated measurement variability limit meaningful rela-
tionships to be explored once 10 dB of threshold loss has
been exceeded or if the RNFL thickness drops below 60 μm
for arcuate field loss (as shown in the flat portion of the
curve in Fig. 2).

In glaucoma studies, the RNFL thickness has been
shown to have a very good sensitivity and specificity for
diagnosing glaucoma, using receiver-operator characteristic
curve analysis. It is important to keep in mind that such
analyses are always influenced by the criteria that are chosen
as the gold standard for the presence or absence of the
disease. Such criteria include the characteristics of the
population being studied, in terms of the distribution of
severity of damage in the population included, and whether
structure (disc appearance) or function (visual field sensi-
tivity and the pattern of loss) is used as the criterion for the
presence of glaucomatous or optic nerve disease.

A great deal of research has also been directed toward
using the RNFL thickness to detect progression of glau-
comatous damage over time. Most of these studies have
applied techniques that have also been used to study
progression of visual field loss, namely, 1) significant change
in RNFL status at a given time point from a prior baseline
measurement or 2) linear regression analysis of RNFL
thickness over time. The main problems encountered in
detecting progression using these approaches are measure-
ment variability and using population statistics to determine
what constitutes a significant change over time. Individuals
appear to vary considerably in the measurement variability
of the RNFL, so applying population statistics (defining the
variability of a given patient by applying the variability from
a population of patients) to a given patient may not be
optimal for individualizing the analysis of progression for
a given patient. In addition, defining a statistically signifi-
cant change over time may not always equate with what is
a clinically significant change—one that would warrant a de-
viation in treatment. This is where monitoring progression
by making use of the structure-function relationship has
distinct advantages. True progression would be expected
to result in a proportional change in both structure (RNFL
thickness) and function (visual field sensitivity), based on
the linear model relating the two, as described previously.
Such an approach also helps to relate changes in structure to
the corresponding function that could be more meaning-
fully related to quality of life measures. Because the rate of
visual field progression in optic neuropathies, such as glau-
coma, varies considerably among treated and untreated
patients and the rate is, in general, slow, the challenge in
the future will be to identify as early as possible which patients are at the most risk for progression and focus aggressive treatment on those patients while not applying the same treatment to patients who are at low risk for significant progression over their remaining life expectancy.

THE MACULAR OCT IN NEURO-OPTHALMOLOGY: ADDED VALUE

For neuro-ophthalmology, the use of the OCT for diagnosis and monitoring of optic nerve disorders pose similar problems as those for glaucomatous optic neuropathy. Further challenges are provided by disorders where optic nerve edema and associated thickening of the RNFL prevent accurate assessment of simultaneous neuronal loss (as discussed in the previous section). In addition, patients with visual field loss but no associated thinning of the RNFL pose a dilemma for the neuro-ophthalmologist because outer retinal disease (e.g., acute zonal occult outer retinopathy [AZOOR]) can mask as vision loss from optic neuropathy, or in some patients with optic neuropathy, insufficient time has elapsed to cause structural loss of neurons in the RNFL or the ganglion cell layer. The following disorders put these issues into perspective and highlight how the macular OCT scan can be used to compliment the RNFL scan and the pattern of visual field loss to arrive at the correct diagnosis and monitoring of their treatment over time:

1. Multiple sclerosis/optic neuritis: In this setting, OCT-based evidence for structural loss (although nonspecific in itself) is being used to help substantiate the clinical diagnosis of multiple sclerosis in the setting of other neurologic or MRI abnormalities. More recently, it has been proposed that OCT might be used as a quantitative tool to monitor the course and treatment of demyelinating disease and predict which patients are likely to progress at a faster rate, requiring a more tailored treatment approach (6–9). There is also evidence that total macular thickness may also reflect neuronal loss in multiple sclerosis (13). In the near future, probability plots relating the pattern of ganglion cell layer thinning with that of the corresponding axon bundles in the RNFL scan and relating this to the pattern of visual field loss will help to better determine areas of significant
The ellipses are the 95% confidence boundaries of the linear model of structure vs function with variability component shown for different levels of glaucoma disease severity; d, expressed in decibels of field loss. Note that for OCT, the within subject repeat measurement variability is fairly constant over the entire range of disease severity, but the repeat within subject variability increases dramatically for visual field sensitivity in the mid range of severity. The interindividual variation in visual field sensitivity is fairly constant, but for OCT, it is highest between subjects that have normal visual field sensitivity. Reproduced with permission from Hood et al (4), copyright © Association for Research in Vision and Ophthalmology, 2010.

3. **Differentiation between NAION and arteritic AION:**
A common problem faced by the neuro-ophthalmologist is whether acute visual loss associated with optic disc edema in an elderly patient is due to giant cell arteritis or NAION. Most clinical investigations focus on the presence or absence of systemic symptoms of giant cell arteritis, the presence of pallid optic nerve edema, the profoundness of the visual field loss, and the presence of acute phase reactants to inflammation in the serum. Fluorescein angiography may also be beneficial in identifying outer retinal ischemia due to occlusion of one or more posterior ciliary arteries if obtained within the first 10 days of vision loss. In this setting, the macular OCT may also be useful for identifying acute loss of photoreceptor structure, particularly whether there is disruption of the inner-outer photoreceptor segment line of increased intensity seen with SD-OCT (15–17). The presence of OCT evidence of outer retinal layer disruption in the context of profound visual loss and optic disc edema would help point toward arteritic AION as the diagnosis differentiating it from NAION.

unaffected by acute axon swelling. In this setting, the macular OCT scan (total thickness and inner ganglion cell layer) has the potential to provide an important adjunct to the RNFL as a structural indicator of therapeutic interventions during the acute stage aimed at preserving neurons.

2. **Nonarteritic anterior ischemic optic neuropathy (NAION):** Similar to optic neuritis, it would be desirable to use OCT to identify treatments aimed at preserving axons, such as steroids, agents that further reduce edema, neuroprotective agents, or treatments aimed at improving oxygenation of the optic nerve during the ischemic state. However, similar to the problems outlined above with acute optic neuritis, the acute edema and associated thickening of the peripapillary RNFL measured with traditional OCT confound the assessment of axon loss during the first 8 weeks, when optic disc edema is still present. The thickness of the macula OCT and ganglion cell layer complex would be expected to provide a better structural indicator of axon preservation or loss compared to the peripapillary RNFL scan. This is because the ganglion cell-inner plexiform layer complex does not become thickened during optic disc edema, as does the peripapillary RNFL. Furthermore, relating the geographic pattern of ganglion cell loss to that of the RNFL and corresponding visual field loss would provide a more powerful means of assessing clinically significant loss of structure and function than just use of either the RNFL or ganglion cell layer thickness alone. In this regard, it will be important in the future to determine how long it takes for the ganglion cell complex to become thinner after irreversible damage to the RNFL, so that clinical assessment and treatment decisions can be made.

pathologic loss of neurons. A recent review has summarized the available evidence relating the loss of retinal structure to the status of demyelinating disease, including evidence for the use of OCT for monitoring progression of demyelinating disease (14). One of the main interest areas at present is whether acute optic neuritis represents a good model for evaluating the efficacy of new central nervous system treatment strategies for multiple sclerosis, such as the use of neuroprotectants, and whether the use of OCT is a valid surrogate for modeling the status of multiple sclerosis and treatment strategy. Since thickening of the peripapillary RNFL is commonly observed by traditional OCT during the acute stage of optic neuritis, where small amount of optic disc edema can be present, the RNFL scan can be misleading when attempting to ascertain whether thinning is due to reduction in edema or due to axon loss over time compared to the acute baseline state. The macular thickness or that of the ganglion cell layer complex may provide a more accurate quantification of the change in ganglion cell number and associated axons over time, relative to the baseline OCT obtained acutely, since it is relatively...
4. **Compressive optic neuropathy**: The presumption in compressive optic neuropathy is that the greater the number of axons that are present at the time of diagnosis, the higher the potential for visual recovery if decompression is successful (5). Here, the confounding variables related to the interpretation of OCT in compressive optic neuropathy lead to the following questions: 1) how much time must elapse before axonal degeneration is detectable on OCT performed at the time of diagnosis and 2) how many neurons/axons are required to support adequate visual function, which may influence treatment decisions? Since the central visual field is commonly affected in compressive optic neuropathy and treatment decisions are weighted more heavily toward the status of the central visual field and corresponding retinal ganglion cells, it would seem logical to monitor the thickness of the ganglion cell layer complex in the macula rather than the thickness of the maculopapillary bundle of the RNFL scan. This is because the maculopapillary bundle is relatively thin in normal eyes and varies between individuals, resulting in less dynamic range from which significant axon loss can be measured. Since the ganglion cell layer is thickest in the macula and perifoveal area, it should provide a better structural target on which to make treatment decisions related to the chance of visual recovery after decompression.

5. **Papilledema**: When the optic nerve appears swollen, the main questions applicable to OCT are as follows: 1) whether true papilledema is present vs pseudopapilledema (18), 2) whether the change in optic disc edema over time can be better quantified using thickening of the RNFL with OCT compared to the fundus appearance of the optic nerve, 3) whether subretinal fluid under the fovea is contributing to vision and visual field loss, and 4) whether axon loss can be detected while the disc is still swollen and differentiated from a reduction in RNFL thickness due to lowering of intracranial pressure. In this respect, the peripapillary RNFL measured with traditional OCT scan poses limitations on the assessment of whether disc edema is becoming less due to reduction of intracranial pressure or whether ongoing axon loss is responsible for the decrease in disc edema. The macular OCT scan and thickness of the retinal ganglion cell layer complex may add much needed clinical information in the setting of chronic papilledema undergoing treatment; if axons are indeed dying off, then the inner layers of the macula will show thinning, but if disc edema is less due to lowering of intracranial pressure and neurons are being preserved, then the inner layers of the macula should not become thinner.

6. **Differentiation of optic neuropathy from retinopathy and identifying disorders in which both are present**: OCT scans of other portions of the posterior pole besides the RNFL can be very revealing. For example, acute or subacute visual field loss with a thickened macula on OCT but without obvious evidence of retinal edema on fundus examination may help point the diagnosis more correctly toward a recent branch or central retinal artery occlusion and shift the diagnostic probability away from anterior or posterior ischemic optic neuropathy, inflammatory, or compressive optic neuropathy. In the chronic state, an abnormally reduced total macular thickness keeping company with a thinned RNFL and pale nerve may also help make the diagnosis of a previous retinal artery occlusion (causing thinning of the ganglion cell layer, inner plexiform layer, and the bipolar cell layer). In such cases, the thinning of the macula is much greater than with optic neuropathy, since the bipolar cell layer usually becomes thinned in addition to the ganglion cell layer and inner plexiform layer. Segmentation of the retinal layers within the macula would help to further differentiate a past retinal artery occlusion from an optic neuropathy without requiring a Ganzfeld or multifocal electroretinogram or neuroimaging. Another example would be a patient with possible neuroretinitis and persistent visual field loss; the combination of an OCT scan of the peripapillary RNFL and macular scan may help reveal the layers of the retina, which are most likely to be the source of pathology explaining the visual field loss. Neuroretinitis usually affects the RNFL, ganglion cell layer, and other layers of the retina, along with the presence of highly reflective exudates seen in the outer plexiform layer in OCT scans of the macula. Most ophthalmologists use the macular OCT to diagnose disorders causing pathology in the inner or outer retina, which cause 1) fluid accumulation in the retina (e.g., cystoid macular edema, diabetic macular edema, vitreal traction, perifoveal telangiectasia, or choroidal neovascular membrane), 2) disruption of the outer layer (e.g., trauma, neovascular membranes, or inflammatory disorders), or 3) macular holes. Such patients often make their way into a neuro-ophthalmology clinic without a certain diagnosis, and a macular OCT may be an important imaging tool for narrowing the differential diagnosis and reducing the cost of an extensive workup for an unknown cause of visual loss. A common presentation might be a patient referred with a diagnosis of optic neuritis but showing an enlarged blind spot or geographic visual field loss not corresponding to a retinal nerve fiber distribution. Such patients may have AZOOR, the big blind spot syndrome, or multiple evanescent white dot syndrome and can be diagnosed with greater certainty if the outer photoreceptor layer shows a disruption of the inner-outer segment line of brightness on SD-OCT. The retinal area of disruption usually corresponds to the location of visual field loss and may be reversible in some cases (15). Other pathologies encountered by a neuro-ophthalmologist that may result in thinning of
the macular OCT or disruption of the photoreceptor structure include hydroxychloroquine (Plaquenil) toxicity (19) and other retinopathies disrupting the photoreceptor layer, including retinitis pigmentosa (16,17).

As discussed above, there are a number of clinical situations that limit the uses of the RNFL OCT scan by itself in aiding the diagnosis of visual loss and assessing change over time. The incorporation of the macular scan acquired by SD-OCT may provide additional information to arrive at the correct diagnosis and in making treatment decisions over time. Although the average total retinal thickness of macular scans can be helpful, the spatial distribution of the thickness into sectors provides even greater information. Many of the newest report printouts from SD-OCT machines show the sector thickness and its relation to age-matched normal scans as a probability plot, similar to an automated visual field. More recently, a posterior pole scan has been introduced in the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), which encompasses approximately 17° radius of retina and which relates the asymmetry between the thickness of small square areas of the superior and inferior retina and also the interocular asymmetry of square areas between the right and left eyes. In addition to the spatial distribution of thickness, the qualitative assessment of its structure in different retinal layers can be very helpful, and additional quantification of the thickness of individual layers would be even more useful to localize which retinal layer is affected by a certain disorder, as shown in Figures 3–5. This has prompted an interest in imaging the source of the axons—the soma of retinal ganglion cells, which predominate in the macula. Accurate quantification of the thickness of each retinal layer would not only provide much needed information on the inner retinal layers but would also provide similar information on the outer retinal layers as a built-in control to provide assurance of the location of the pathology. Here, the question is how to best take advantage of the added resolution and spatial sampling offered by SD-OCT so that the ganglion cell layer can be accurately quantified to reflect the number of neurons present. This also presupposes that imaging of the ganglion cell layer in the macular region provides adequate spatial sampling to reflect the status of disease affecting not only the macula but also regions peripheral to it.

**SEGMENTATION OF THE GANGLION CELL LAYER WITHIN THE CENTRAL MACULA WITH SD-OCT AND ITS POTENTIAL ADVANTAGES**

1. The retinal ganglion cells are densest in the macula and form a stratified multicellular layer within the central 6°.
of visual field. Therefore, loss of axons and the corresponding soma in this location is likely to cause a thinning of the retinal ganglion cell layer.

2. The lack of large retinal vessels in this location makes their confounding contribution to the thickness of the ganglion cell layer very minimal compared to the peripapillary retina, where they do influence the RNFL measurement.

3. The mapping of visual field location to corresponding ganglion cell soma is less complicated than the situation with the RNFL bundles and may show less interindividual developmental variability. Simplistically, a focal light in the macula activates the ganglion cells directly underlying it. In the foveal and perifoveal location, this is not strictly the case, and some modification has to be made in this area of the visual field due to displaced ganglion cells.

4. Recent advances in OCT image analysis using both manual (15) and automated analysis in 3 dimensions (16,19) have provided a potential solution for delineation of the different neuronal layers in the macula (Figs. 3, 4).

5. Preliminary attempts to quantify the correlation between visual threshold and retinal ganglion cell thickness in the macula appear to subjectively correlate with the spatial pattern of visual field loss in the macula in patients with glaucoma (Fig. 5) and AION. However, a quantitative
correlation between ganglion cell thickness and corresponding overlying visual threshold has not yet been reported in detail.

**CHALLENGES ASSOCIATED WITH OCT ANALYSIS OF THE MACULA TO BE OVERCOME BEFORE CLINICAL MONITORING OF OPTIC NERVE FUNCTION IS USEFUL**

1. Current commercially available OCT and associated software are not capable of segmenting the ganglion cell layer in 3 dimensions. At best, some manufacturers segment the inner layers of the retina of the macula as a neural complex layer (RNFL, ganglion cell layer, and inner plexiform layers), but this software analysis has not yet been rigorously validated. Recently, Hood et al reported to have manually segmented 2-dimensional line scans through the macula and have shown correlation of thinning of the ganglion cell + inner plexiform layer with corresponding loss of visual threshold in glaucoma, so this approach does have promise (20). Our group has reported automated segmentation of retinal layers using a 3-dimensional graph search approach applied to volume OCT scans, as shown in Figures 3–5 (21,22).

2. Outside of the central 6° of the macula, the ganglion cell layer is less of a multicellular layer. In areas where there is only a single layer of ganglion cells, it is not known if loss of soma will cause a measurable significant thinning of the cellular layer or whether it will just be replaced by glial and Mueller cells, making structural thinning of the ganglion cell layer of the inner retina difficult to measure (4).

3. Focal peripheral visual field damage would be unlikely to affect the retinal ganglion cell layer in the macula, making it theoretically less sensitive to detection and monitoring of peripheral field pathology. However, most optic nerve diseases do show some degree of diffuse loss, and although significant abnormalities in visual threshold may not be detected, there still may be a measurable decrease in retinal ganglion cell thickness in the macula, even though a visual field test may appear to show mainly extramacular loss of sensitivity.

4. It is currently not known how much time it takes for a decrease in the thickness of the ganglion cell layer to occur after damage to the optic nerve at different distances from the globe. The time delay between permanent damage and atrophy of the ganglion cell layer would provide a framework for dating the time of injury.

In summary, recent improvements in OCT resolution and automated segmentation software has provided a means of relating visual pathway damage to structural changes in the RNFL and corresponding some of the ganglion cells in the inner layers of the macula and in the outer photoreceptor layer in the macula. These advances further our ability to differentiate and localize ambiguous causes of vision loss and visual field defects in neuro-ophthalmology. Ganglion cell layer analysis in volume OCT data may provide yet another piece of the puzzle to understanding structure-function relationships and its application to diagnosis and monitoring of optic nerve diseases, while similar structure-function relationships are also being elucidated in the outer retina for photoreceptor diseases.

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Abstract: Visual dysfunction is one of the most common clinical manifestations of multiple sclerosis (MS). Just over a decade ago, MS clinical trials did not include visual outcomes, but experts recognized the need for more sensitive measures of visual function. Low-contrast letter acuity emerged as the leading candidate to measure visual disability in MS, and subsequent studies found low-contrast acuity testing to correlate well with brain MRI lesion burden, visual-evoked potentials, quality of life (QOL), and retinal nerve fiber layer (RNFL) loss, as measured by optical coherence tomography (OCT). OCT in MS has allowed for assessment of structure-function correlations that make the anterior visual pathway and acute optic neuritis (ON) ideal models for testing novel agents for neuroprotection and repair. New therapies that reduce axonal loss by neuroprotective or myelin repair mechanisms can now be assessed noninvasively by OCT and coupled with visual function data. Based on OCT studies in MS, RNFL thickness is reduced significantly among patients (92 μm) vs controls (105 μm) and is particularly reduced in MS eyes with a history of ON (85 μm). Worsening of visual function by a clinically significant ≥ 7 letters or approximately 1.5 lines for low-contrast acuity is associated with approximately 4.5 μm reductions in RNFL thickness in MS eyes. Longitudinal studies of OCT have also shown RNFL axonal loss over time that occurs even in the absence of acute ON and that correlates with clinically meaningful worsening of vision and QOL, even in patients with benign MS. The latest OCT investigations involve high-resolution spectral-domain (SD) OCT with segmentation and measurement of specific retinal layers using computerized algorithms. These methods allow quantitation of ganglion cell (neuronal) layer loss and axonal degeneration in MS in vivo. In this review, we examine the data from these studies and ongoing trials that highlight the entity of ON as a model to investigate neuroprotection and neurorepair. In doing so, we also present representative group data from studies that have examined visual function, OCT measures, and QOL scales in patients with MS and ON and disease-free controls. These data, and those from recent meta-analyses, may be used to provide reference values for the development of clinical trial protocols.

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Visual loss has been recognized for decades as one of the most common and disabling clinical manifestations of multiple sclerosis (MS). It was not until a decade ago, however, that MS clinical trials began to include sensitive measures of visual function. Inspired by the effective use of contrast sensitivity (Pelli-Robson charts) to demonstrate visual abnormalities in the Optic Neuritis Treatment Trial (ONTT) (1–6), low-contrast letter acuity was introduced into MS trials as an exploratory outcome to better capture the often subtle visual symptoms experienced by patients with acute optic neuritis (ON) (7–10).

Visual symptoms can result from a variety of pathological processes, including inflammation, demyelination, and axonal degeneration in the afferent visual pathway (retina, optic nerves, chiasm, and tracts) (11–15). During the past decade, the contributions of axonal and neuronal loss to disability in MS have been increasingly recognized (12,16–19). Developed initially as a noninvasive tool to monitor retinal disease and glaucoma, optical coherence tomography (OCT) was first applied to cohorts of patients with MS and ON over a decade ago to provide validation of clinical visual outcomes and to capture anterior visual pathway axonal loss (15,20–25). As a result of these early studies...
and >100 subsequent published investigations of OCT in MS and ON (26), the visual pathway is now recognized as a model for structure-function correlation in MS for studying the pathophysiology of disease and for testing both novel and standard therapies that involve neuroprotection and repair. OCT can be used noninvasively to capture reductions in axonal loss that may be associated with neuroprotective or myelin repair therapies; this information can be correlated with visual function and quality of life (QOL) data to further establish the clinical relevance of these structural outcomes.

OCT enables investigators to rapidly and reproducibly evaluate the structural composition of the retina. Ultimately, OCT could substantially increase our understanding of the mechanisms of tissue injury in MS, ON, and other optic neuropathies.

A decade after publication of the first studies of low-contrast acuity in MS, this test and OCT measures are commonly used in MS clinical trials. They have formed the foundation for new trials that use acute ON as a model for identifying novel compounds for neurorepair (27–32).

This review describes a number of advancements in the development of visual function outcomes in MS and OCT as a novel technology that enables objective analysis of the processes of neurodegeneration. In addition, we present representative group data from studies that have examined visual function, OCT measures, and QOL scales in patients with MS and ON and disease-free controls (Table 1). These data may be used to provide initial reference values and should be viewed in the context of 1) the continually evolving field of vision in MS, 2) the potential challenge inherent in applying group data to individual patients, and 3) the perspective that even the small observed differences in mean OCT values have been shown to correlate with clinically meaningful changes in visual function and QOL in MS patients.

VISION IN MS: THE STORY

In the late 1990s, the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force developed the Multiple Sclerosis Functional Composite (MSFC) in response to the need for more sensitive neurologic outcome scale (33,34). Designed to be a battery of performance measures complementary to the Expanded Disability Status Scale (EDSS), the MSFC includes the 25-Foot Timed Walk, the 9-Hole Peg Test, and Paced Auditory Serial Addition Test (35–38). While multidimensional, the MSFC did not include a measure of visual function. In the evaluation of candidate MSFC visual components from MS clinical trial data used to develop the MSFC, Snellen high-contrast visual acuity (VA) did not change over time or demonstrate concurrent changes with EDSS scores (33). Contrast sensitivity, as tested by line gratings and letter charts in MS and by Pelli-Robson charts in the ONTT, had been shown to be a sensitive measure of afferent visual function, even among patient with Snellen acuities of 20/20 or better (1–6,39–43). Importantly, measures of low-contrast vision are predictive of "real-world" visual tasks, such as reading rate, facial recognition, and driving (44).

Low-Contrast Letter Acuity

While used successfully in the ONTT to demonstrate persistent visual abnormalities beyond recovery of high-contrast VA, Pelli-Robson contrast sensitivity charts were not available for purchase in 1998, when the first MS clinical trial to incorporate a low-contrast visual measure as an exploratory outcome was begun. This trial, International MS Progressive Avonex Clinical Trial (IMPACT), incorporated low-contrast Sloan letter charts (7,8,45,46). These charts are the low-contrast (gray letters on white) “cousin” of the Early Treatment Diabetic Retinopathy Study (ETDRS) high-contrast VA charts used in ophthalmology clinical trials (Fig. 1). Sloan charts have a standardized format based on the ETDRS VA charts. Three contrast levels have been used in MS trials and research studies, including 100% (high-contrast, used to measure VA as a descriptor of the study cohorts), 2.5%, and 1.25% (lightest contrast level). Charts are scored letter by letter, and numbers of letters identified correctly constitute the score for each chart (Table 1). Most recently, visual improvement and loss by the low-contrast acuity chart has been defined as a 7-letter change in score, while 5-letter changes in high-contrast VA are now considered clinically significant for patients with good VA (47). This threshold represents a change that exceeds that which would be expected from repeated testing when there was no real change (45,48) and to correlate with retinal nerve fiber layer (RNFL) axonal loss in patients with MS (47). As shown in Table 1, differences in mean letter scores for MS vs disease-free control groups are consistently ≥5 letters for VA and ≥7 letters for low-contrast acuity. Since the 5- and 7-letter criteria are meant to be applied to individual eye or patient differences, differences in mean scores of such magnitude are therefore likely to be clinically meaningful. Furthermore, these 5- and 7-letter mean changes have been shown to correlate significantly with vision-specific and overall QOL, as well as structural measures of OCT RNFL thickness. These associations of OCT and QOL measures with clinically meaningful changes in visual function provide perspective for the data in Table 1, despite the seemingly small magnitudes of differences in means for OCT values.

In the IMPACT trial and in heterogeneous MS cohorts (7,8,45), low-contrast letter acuity was shown to be a highly reliable (high intraclass correlations of 0.86–0.95) and practical method that was superior in identifying MS-related visual loss compared to other available tests (Fig. 2). Correlations of Sloan chart scores with MSFC and EDSS in these studies were significant and moderate in magnitude (r = 0.56 vs MSFC; r = −0.43 vs EDSS, P < 0.0001). These studies
<table>
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<th></th>
<th>Disease-Free Controls</th>
<th>All MS</th>
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<th>MS, History of ON</th>
<th>References for Data*</th>
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<td><strong>High-contrast VA, ETDRS, number of letters correct</strong></td>
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<td>Binocular testing</td>
<td>64 ± 5 (n = 61 eyes)</td>
<td>59 ± 8 (n = 239 eyes)</td>
<td>60 ± 6 (n = 150 eyes)</td>
<td>58 ± 9 (n = 87 eyes)</td>
<td>103* (22,47,56,81,84)</td>
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<td>Low-contrast letter acuity (2.5%), number of letters correct</td>
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<tr>
<td>Binocular testing</td>
<td>66 ± 5 (n = 324 pts)</td>
<td>62 ± 8 (n = 1,007 pts)</td>
<td>63 ± 7 (n = 544 pts)</td>
<td>61 ± 10 (n = 463 pts)</td>
<td>56* (7–10,51)</td>
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<td>96 ± 4 (n = 31 pts)</td>
<td>88 ± 13 (n = 122 pts)</td>
<td>90 ± 12 (n = 111 pts)</td>
<td>85 ± 14 (n = 51 pts)</td>
<td>103* (49–51,56)</td>
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<td>10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25, best score = 100</td>
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<td>97 ± 3 (n = 31 pts)</td>
<td>87 ± 13 (n = 122 pts)</td>
<td>88 ± 12 (n = 111 pts)</td>
<td>83 ± 14 (n = 51 pts)</td>
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<td><strong>Peripapillary RNFL thickness, μm</strong></td>
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<td>104.5 ± 10.7 (n = 219 eyes)</td>
<td>92.5 ± 16.7 (n = 1,058 eyes)</td>
<td>95.6 ± 14.5 (n = 730 eyes)</td>
<td>85.7 ± 19.0 (n = 328 eyes)</td>
<td>81* (20–22,47,70–84)</td>
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<td><strong>Total macular volume, mm³</strong></td>
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<td><strong>Peripapillary RNFL thickness, μm</strong></td>
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<td>88.9 ± 6.9 (n = 61 eyes)</td>
<td>84.1 ± 8.4 (n = 239 eyes)</td>
<td>87.0 ± 6.6 (n = 150 eyes)</td>
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<td><strong>Macular RNFL, μm</strong></td>
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<td></td>
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<td>25.5 ± 7.1 (n = 150 eyes)</td>
<td>20.0 ± 9.0 (n = 87 eyes)</td>
<td>103* (96,105)</td>
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*Reference with asterisk is source of data presented in table; references that contain similar data are in parentheses.

pts, patients; SD, spectral-domain (Cirrus platform); TD, time-domain (OCT-3 platform).
Logistic regression analyses demonstrating capacity for each visual function test to predict MS vs disease-free control status in a heterogeneous MS cohort, accounting simultaneously for age. Odds ratios in favor of participants with worse vision scores being MS patients (vs disease-free controls) were greatest for low-contrast letter acuity (Sloan charts) and contrast sensitivity (Pelli-Robson chart). These measures thus best distinguish MS patients from disease-free control subjects, even after accounting for age differences between the 2 groups. VF, visual field. Reprinted with permission from Balcer et al (7) (copyright © 2003 AAN Enterprises, Inc.).

Vision-Specific QOL Measures

The relevance of low-contrast letter acuity measurements to patient functioning has been underscored by studies linking these scores to vision-specific QOL. Scores for the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) are reduced among patients with MS (Table 1) (49–51). A 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 has also been designed using MS cohorts to capture symptoms relevant to neurologic disease. In a recent study of 167 patients with MS, 2-line differences in visual function by low-contrast acuity are associated, on average, with >4-point worsening (6.7 – 10.9 points, $P < 0.001$ accounting for age) in NEI-VFQ-25 composite (overall) score, reductions that are considered to be clinically meaningful based on ophthalmic epidemiologic studies (52–55). In Table 1, the differences in mean scores between MS patients and disease-free controls were $\geq$4 points; such differences may be considered clinically significant for both individual changes and group data. Binocular scores for low-contrast acuity also correlated significantly with score for the 10-Item Neuro-Ophthalmic Supplement ($P < 0.001$), the Impact of Visual Impairment Scale ($P < 0.001$), and the...
SF-36 Physical Component Summary ($P < 0.001$) in this MS cohort. Collectively, these data demonstrated that low-contrast acuity testing provides information on patient-reported aspects of vision. This is a key feature for clinical measures and a prerequisite for their use as primary outcomes in clinical trials.

**Binocular Summation of Acuity**

While the earliest studies of low-contrast acuity and QOL examined binocular vision scores (vision testing with both eyes together), monocular measurements (with each eye separately) have more recently been introduced into MS trials and vision research with the inclusion of OCT scanning as a structural correlate to vision (Table 1). Given the importance of both of these types of acuity to measurements of function, analyses of MS cohort data, including both binocular and monocular scores, were performed to examine the relation between the two and to determine the potential roles for binocular summation and inhibition (56). Binocular summation of acuity occurs when vision is improved under binocular viewing conditions (binocular score is greater than the scores for either eye alone) (57). In contrast, patients with binocular inhibition have worse binocular vision compared to the better eye alone. Among 1,07 patients with MS and 324 disease-free controls, binocular summation was substantial (5- to 7-letter increases over better eye acuity, 28%–52% with >7 letters, $P < 0.001$) for low-contrast acuity at the 2.5% and 1.25% levels. For high-contrast VA, only 3.0%–3.4% of patients showed similar degrees of summation. Increasing age ($P < 0.0001$), greater interocular differences in acuity ($P < 0.0001$), and history of ON ($P = 0.015$) were associated with lower magnitudes of binocular summation; in fact, some of these patients had binocular inhibition. Importantly, greater degrees of binocular summation were predictive of better QOL by the NEI-VFQ-25 ($P = 0.02$) and 10-Item Supplement ($P = 0.03$), indicating that the capacity to use both eyes together is an important factor in determining how well patients with MS can perform daily activities (56).

**Relation of Vision to MRI and Visual-Evoked Potentials**

Correlation with biological markers and electrophysiological measures of disease is one of the most important factors in the evaluation of clinical outcome measures such as low-contrast letter acuity. The first such study determined the relation of binocular low-contrast scores to brain MRI measures of T2 lesion burden (58). This study of 45 patients with MS found that those with worse low-contrast acuity scores had greater T2 lesion volumes in whole brain (3 mm$^3$ increase for every 1-line worsening, $P = 0.002–0.004$, accounting for age and disease duration). Area 17 and optic radiation white matter lesion burden specifically correlated with visual function, but non–vision-related white matter did not show associations. These findings were important in providing a structural correlate to low-contrast acuity scores and also in emphasizing a potential postgigulate pathway component to binocular low-contrast vision.

Standard brain MRI techniques have provided information regarding disease burden in MS. However, the capacity for these techniques to precisely quantify axonal and neuronal loss, particularly in the anterior visual pathway, has been limited. Electrophysiologic markers such as the visual-evoked potential (VEP) can provide additional information on anterior visual pathway integrity. Recent studies have combined assessments of vision loss with VEP. Conventional VEPs measure the cortical response to monocular stimulation in the central 30° of the visual field. In MS, the latency characteristically is delayed with normal amplitude. Axonal loss, however, can reduce this amplitude (59). Abnormal VEPs in unaffected eyes provided evidence for clinically silent lesions in the optic nerve that might help identify dissemination in space and help establish the diagnosis of MS (60). Various studies have shown that contrast sensitivity can be measured by VEP (43), and in MS, low-contrast stimuli VEPs show increased latencies or absent waveforms when compared with high-contrast stimuli VEPs. Low-contrast VEP may prove to be helpful in identifying demyelination (61). Other studies have concluded that multifocal VEP provides higher sensitivity and specificity in detecting abnormalities in visual function in MS and in ON (62).

Naismith et al (63) systematically evaluated the utility of OCT and VEPs to detect the presence of clinical and subclinical ON and examined the relation of these measures to visual function. This retrospective cross-sectional study evaluated 65 subjects (n = 96 eyes) with MS (n = 40), clinically isolated syndrome (CIS, n = 1), neuromyelitis optica (n = 20), and idiopathic demyelination (n = 4). Patients had at least one episode of ON ≥6 months prior to enrollment. VEPs detected ON in 81% of patients (32% of subclinical ON in unaffected eyes and 75% of all subclinical ON). In contrast, using their criteria, they found that OCT identified 60% of eyes with ON and less than 20% of subclinically affected eyes. The authors concluded that OCT is less sensitive than VEPs in ON. On the other hand, to the extent that this study focused on patients with relatively poor vision, there were likely floor effects with regard to OCT RNFL thickness.

**STRUCTURE-FUNCTION CORRELATIONS: OCT**

Although acute ON and demyelination are important contributors to visual dysfunction, irreversible axonal and neuronal degeneration are also final common pathways to permanent visual loss (12–14,24,64). While the relationship between visual loss and brain MRI lesion burden discussed above is a relatively new finding, the extremely
high predilection for MS to involve the optic nerves is well-documented and was initially observed long before the advent of advanced optical and neuroimaging. Autopsy studies have shown that up to 94%–99% of MS patients have detectable optic nerve lesions (65,66). Subclinical changes related to visual loss may involve the optic nerves or chiasm, or postchiasmal regions of the optic tract (13,67–69).

Features and Advantages of OCT Imaging

OCT provides a noninvasive technique to measure axonal and neuronal loss in the anterior visual pathways (24,28–32). As the optical analog of ultrasound B-mode imaging, OCT allows us to image the RNFL (15,20–32,47,59,70–82). Since, within the retina, these axons are nonmyelinated, the RNFL is an ideal structure to visualize the processes of neurodegeneration, neuroprotection, and potentially even neurorepair. In contrast to the peripapillary RNFL, which contains axons, the macula contains a large proportion of retinal ganglion cell neurons (about 34% of total macular volume) (81). The development of Fourier-domain (or spectral-domain [SD]) detection has in particular enhanced ophthalmic OCT technology. While many of the studies cited in this review utilized time-domain (TD) OCT, some have incorporated the newer SD-OCT technologies. Table 1 presents some representative group data for OCT measures in patients with MS, ON, and disease-free controls. Since OCT measures have been shown to correlate with clinically meaningful changes in visual function and QOL (see above), the differences in mean values between groups shown in Table 1 are likely to have clinical significance. Larger studies and additional meta-analyses will allow us to further refine the precision of these representative average values.

OCT Investigations in MS and ON

The earliest application of OCT technology to the study of MS was reported by Parisi et al in 1999 (15). In this study, which utilized first-generation OCT technology, 14 patients with MS who had completely recovered from a previous event of acute ON were analyzed. The thickness of the RNFL was shown to be reduced by 46% in the affected eyes of the patients with MS vs the control eyes (P < 0.01) and by 28% when affected eyes were compared with the “unaffected” eyes of the same patient (P < 0.01). Even in the clinically unaffected eyes of patients, however, there was a 26% reduction in RNFL thickness when compared with control eyes (P < 0.01).

In 2005, Trip et al (21) reported their observations with OCT in 11 patients with MS and 14 patients with CIS, all of which individuals had a history of a single episode of ON. The study was a cross-sectional analysis with follow-up ranging from 1 to 9 years after the ON event. Corroborating the previous findings by Parisi et al (15), the investigators found a 33% reduction in RNFL thickness in the eyes of the patients when compared with the eyes of matched controls and a 27% reduction when the affected and unaffected eyes of the same patient were compared (P < 0.001). Trip et al (21) extended the utility of OCT by also showing that the macular volume (a reflection of retinal ganglion cell neuronal integrity) was reduced by 11% in the eyes of patients with a history of ON when compared with control eyes (P < 0.001) and by 9% in the affected vs the unaffected eye of the same patient (P < 0.001).

In 2006, Costello et al (20) reported that the majority of patients with MS who have ON (approximately 75%) will sustain 10–40 µm of RNFL loss within a period of approximately 3–6 months. This finding is striking given that the RNFL is only about 110–120 µm thick by the age of 15 years and that most individuals (without a history of glaucoma or macular degeneration) will lose only about 0.017% per year in retinal thickness, which equates to approximately 10–20 µm over 60 years (25,83). Costello et al (20) also provided compelling evidence identifying an injury threshold within the RNFL of about 75 µm; thinning of the RNFL below this level led to a corresponding decline in visual function, as measured by automated perimetry. Using low-contrast letter acuity in MS eyes with a history of acute ON, we have found a similar threshold for abnormal visual function and axonal loss at 80 µm (Fig. 3).

The trajectory and time course of RNFL axonal loss following an episode of acute ON are important for determining the “window of opportunity” within which a neuroprotective or repair agent should be administered in a treatment trial. Sample size calculations for a

![Abnormal low-contrast acuity (2.5%) vs Normal low-contrast acuity (2.5%)](image)

FIG. 3. Scatter plots showing relation of low-contrast letter acuity to RNFL thickness (in micrometers) for eyes from a heterogeneous MS cohort (n = 82) with a history of acute ON. The left panel shows eyes with abnormal low-contrast acuity scores, defined as 7 letters below the mean of a disease-free control group. Eyes in the right panel have normal low-contrast acuity at 2.5% contrast. Among eyes with abnormal low-contrast acuity, worse scores were significantly associated with lower (thinner) peripapillary RNFL, accounting for age and adjusting for within-patient intereye correlations.
One of the most important findings that has resulted from the use of OCT MS studies is the correlation between RNFL thinning and visual loss, as measured by low-contrast letter acuity. In 2006, Fisher et al (22) conducted a cross-sectional study that compared RNFL thickness among MS eyes with a history of ON (MS ON eyes), MS eyes without a history of ON (MS non-ON eyes), and disease-free controls. In addition to OCT measurement of OCT, they conducted low-contrast visual assessments with low-contrast letter acuity, contrast sensitivity (Pelli-Robson charts), and high-contrast VA (ETDRS charts). The authors found that RNFL thickness was reduced significantly among MS patients (92 μm) vs controls (105 μm, P < 0.001) and particularly reduced in MS ON eyes (85 μm, P < 0.001). Furthermore, lower visual function scores were associated with reduced average overall RNFL thickness in MS eyes; for every 1 line decrease in low-contrast letter acuity or contrast sensitivity score, the mean RNFL thickness decreased by 4 μm. These findings not only supported the validity of low-contrast visual assessment as a secondary clinical outcome measure in MS trials, they also suggested a potential role for OCT in trials that examine neuroprotective and other disease-modifying therapies. Several other investigations have demonstrated correlations between RNFL thinning and visual loss (21,25,77,85–87).

While the above studies used cross-sectional studies to examine relationships between biomarkers measured with OCT and visual function, the first longitudinal study to study the relationship between RNFL thickness and visual loss was carried out by Talman et al in 2010 (47). These investigators used OCT to measure RNFL thickness at baseline and at 6-month intervals during a mean follow-up of 18 months at 3 centers. Low-contrast letter acuity (2.5% and 1.25%) and high-contrast VA were tested. The results indicated that among 299 patients (593 eyes) with at least 6 month follow-up, eyes with visual loss showed greater RNFL thinning compared to eyes with stable vision (low-contrast acuity, 2.5%: P < 0.001; VA: P = 0.005). RNFL thinning increased over time, with average losses of 2.9 μm at 2–3 years and 6.1 μm at 3–4.5 years (P < 0.001 vs 0.5–1 year follow-up). The authors concluded that progressive RNFL thinning occurs as a function of time in some patients with MS, even in the absence of ON (47). Studies such as this is a major contribution to our understanding of the MS disease process.

Recently, OCT has also been used to show the capacity of RNFL thinning to distinguish MS disease subtypes. Costello et al (85) found that RNFL comparisons involving eyes without ON yielded greater differences between MS subtypes than ON-affected eyes. Overall RNFL values in nonaffected eyes were reduced in patients with secondary progressive multiple sclerosis (SPMS) (83.4 μm), relative to ON as a CIS (101.2 μm) (P = 0.0009), and patients with relapsing-remitting multiple sclerosis (RRMS) (103.7 μm) (P = 0.001); and temporal RNFL atrophy was greater in RRMS (64.4 μm) eyes as compared to CIS eyes (73.2 μm, P = 0.02). In ON-affected eyes, RNFL atrophy was greater in patients with SPMS (39.5 μm) than those with CIS (58.1 μm, P = 0.03) and in patients with RRMS (48.2 μm) relative to those with CIS (P = 0.05). These authors concluded that RNFL thickness might represent an important MS structural marker because RNFL thinning reflects disease progression.

While RNFL thinning is most marked in patients with SPMS, those with benign MS, traditionally defined as EDSS ≤3 and ≥15 years of disease duration, are thought to follow a milder course (88). We recently conducted an analysis of a longitudinal MS cohort to determine the extent of visual pathway axonal loss by OCT RNFL thickness. At 3 academic centers, a subset of patients with EDSS scores, visual function, OCT, and QOL assessments was analyzed. Low- and high-contrast letter acuities were performed to assess visual function. RNFL thickness was determined using OCT-3. QOL scales included the NEI-VFQ-25 and SF-36. Among 68 patients (135 eyes) studied longitudinally, 13 (26 eyes) had benign MS using criteria of EDSS ≤3 and ≥15 years of disease duration. Benign MS eyes had as much RNFL thinning (−3.6 μm, P = 0.0008 vs baseline, paired t test) as typical MS eyes (−3.3 μm, P < 0.0001).
Both groups had significant low-contrast acuity loss over time. History of ON was more frequent in benign MS (69% vs 33% of eyes). History of ON distinguished benign vs typical MS ($P = 0.002$) and correlated with RNFL thickness at baseline ($P = 0.002$) and disease duration ($P = 0.03$) but not EDSS ($P = 0.32$, logistic regression). NEI-VFQ-25 scores were also worse for benign MS, accounting for age ($75 \pm 21$ vs $88 \pm 11$, $P = 0.005$). These findings demonstrated that patients with benign MS have RNFL axonal loss that is as marked as that of typical MS and have reduced vision and QOL. While overall neurologic impairment is mild, visual dysfunction, not well-captured by the EDSS, accounts for a substantial degree of disability in benign MS.

**The Future of OCT in MS: Retinal Segmentation**

In addition to axonal degeneration, neuronal loss is increasingly recognized as a correlate of disability in MS (16–19,89–91). While investigations of TD-OCT have shown reductions in total macular volume as a potential marker for neuronal loss in MS eyes, more specific measurement of the retinal ganglion cell layer (GCL) and other layers by segmentation has only recently emerged following the introduction of high-resolution and high-speed-domain (SD) OCT techniques to study MS (Table 1) (25–27,82,92–100). Earlier studies of total macular volume using TD-OCT suggested that retinal ganglion cell neuronal loss occurs in MS eyes and that this correlates with visual function (81). These observations were necessarily based on the structural assumption that approximately 34% of the total macular volume is comprised of ganglion cells.

Using SD-OCT, some of the first observations of specific retinal GCL loss in MS eyes were generated by a study that involved manual delineation of the GCL on a Spectralis OCT platform (Fig. 4) (97). In this pilot investigation, eyes of patients with MS ($n = 16$) had significantly lower GCL volumes than control eyes ($P < 0.001$, accounting for age and within-patient intereye correlations). Lower volumes were noted among MS eyes with a history of ON ($n = 4$) compared with MS non-ON eyes ($P < 0.001$). Reduced GCL volumes were not associated with worse high-contrast VA ($P = 0.14$), but did predict visual loss by low-contrast acuity ($P = 0.003$).

While manual OCT retinal segmentation demonstrated important findings in these studies, the labor-intensive nature of this technique (approximately 2 hours per eye) limits its large scale use in MS cohorts. Computerized segmentation algorithms have been used successfully in studies of glaucoma (99,100) and have provided the basis for 2 recent investigations in MS cohorts. Saidha et al (96) used a segmentation method developed commercially to study patients with a macular thinning predominant (MTP) MS phenotype. These patients have peripapillary RNFL thickness that is within the normal ranges but exhibit severe <5th percentile thinning of the macular region on SD-OCT. This group of patient eyes demonstrated thinning of the outer retinal layers ($P < 0.001$ for inner and outer nuclear layers in MTP vs MS eyes), with relative sparing of the GCL. Patients with the MTP phenotype also had relatively greater degrees of overall neurologic disability, suggesting that these individuals may have a distinct or primary process underlying their neuronal loss.

Recent pathologic studies of postmortem eyes from heterogeneous MS cohorts ($n = 82$) demonstrated that the GCL is a site of neuronal dropout in 79% of eyes (101). Retinal ganglion cell loss has also been shown to occur in vivo in mouse models of relapsing-remitting experimental autoimmune encephalomyelitis with optic nerve involvement and to be reduced by neuroprotective therapies, such as resveratrol, in these models (102). To examine GCL loss in MS in vivo in patients with MS, our collaborative MS vision research group has used a novel computerized...
segmentation algorithm developed at the University of Pittsburgh (103). In this study, patients with MS (n = 122 subjects, 239 eyes) and disease-free controls (n = 31 subjects, 61 eyes) underwent Cirrus SD-OCT (Carl Zeiss-Meditec, Dublin, CA). Images were captured using Macular Cube (200 x 200 or 512 x 128) and ONH Cube 200 x 200 scanning protocols. Retinal layer segmentation was performed using algorithms originally designed for studies of glaucoma. Thicknesses of the GCL/inner plexiform layer (GCL+IPL), RNFL, outer plexiform/inner nuclear layer, and outer nuclear/photoreceptor layer were measured and compared in MS vs control eyes as well as MS ON vs non-ON eyes. Since the IPL is a thin layer that is currently inseparable from the GCL using OCT, the combination GCL+IPL is used to estimate GCL thickness. Macular RNFL and GCL+IPL were significantly decreased in MS subjects vs controls (P < 0.001, P = 0.001) and in MS ON eyes vs non-ON eyes (P < 0.001 for both measures). Peripapillary RNFL, macular RNFL, and GCL+IPL were all significantly correlated with VA (P ≤ 0.001), 2.5% low-contrast acuity (P < 0.001), and 1.25% low-contrast acuity (P ≤ 0.001). Among OCT measurements, reductions in GCL+IPL (P < 0.001) and macular RNFL (P = 0.006) were the most strongly associated with lower (worse) NEI-VFQ-25 and 10-Item Supplement composite scores for QOL; GCL+IPL thinning was significant even accounting simultaneously for macular RNFL thickness (P = 0.03 for GCL+IPL and P = 0.39 for macular RNFL). These data demonstrate that GCL+IPL thinning is most significantly correlated with both visual function and vision-specific QOL in MS. GCL thickness is likely to emerge as a useful structural marker of disease. These findings parallel those of MRI studies that show gray matter disease as a marker of neurologic disability in MS.

**Vision and OCT in MS Clinical Trials: Role for Reading Centers**

The incorporation of OCT and visual outcome measures into MS clinical trials has benefited from the presence of OCT reading centers. The University of California Davis Reading Center recently published the results of Stratus (TD) OCT quality control in 2 multicenter MS clinical trials (104). The authors evaluated 19,961 OCT scans from 981 patients with the goal of determining the influence of OCT quality control procedures on error rate. In Trial 1 (design and therapeutic agent not specified in publication), there was no ophthalmic technician certification and data were obtained by the Reading Center retrospectively. However, in Trial 2, technicians were certified and submitted data prospectively according to the study protocol. OCT scans in Trial 2 had higher signal strengths, fewer errors, and more usable data compared to Trial 1 scans. This study showed that certified technicians and prompt transmission of data for ongoing quality control monitoring provide higher data quality; these factors and the use of Reading Centers should be considered in the design of clinical trials for MS and other neuro-ophthalmologic disorders.

**CONCLUSIONS**

Visual dysfunction is not only an important contributor to impairment and disability in MS but represents a unique opportunity for studying disease mechanisms and for testing new therapies that involve neuroprotection and repair. The advent of ocular imaging with OCT has allowed investigators to examine in vivo the morphological changes that accompany visual loss. Sensitive visual function tests, including low-contrast letter acuity, have been shown to correlate with OCT measures of axonal and neuronal loss as well as with patient-reported assessments of QOL. These observations have been instrumental in the establishment of a structure-function paradigm for using the anterior visual pathway as a model in MS. Low-contrast letter acuity, vision-specific QOL measures (NEI-VFQ-25 and 10-Item Neuro-Ophthalmic Supplement), and OCT measures have been incorporated into recent MS clinical trials. It is likely that these emerging data will yield important findings for therapeutics in MS, ON, and other neuro-ophthalmologic causes of visual loss.

**REFERENCES**


Stenting of the Transverse Sinuses in Idiopathic Intracranial Hypertension

Rebekah Ahmed, MBBS, Deborah I. Friedman, MD, MPH, G. Michael Halmagyi, MD, FRACP

Venous Hypertension and Increased Intracranial Pressure

Although the mechanism of idiopathic intracranial hypertension (IIH) is uncertain, the cerebral venous system has been implicated since the 1930s. Dandy (1) hypothesized that the volume of cerebrospinal fluid (CSF) or cerebral blood might be increased. Others postulated that the cerebral microvasculature was the source of cerebral edema in this condition (2–4). Intracranial venous hypertension was subsequently proposed as a unifying mechanism or final common pathway of IIH. Johnston and Paterson (5) first suggested that increased sagittal sinus pressure causing decreased CSF absorption was the underlying cause of IIH.

A syndrome clinically identical to IIH is produced by cerebral venous sinus thrombosis (6–8). Interest in the dural venous sinuses as the source of increased intracranial pressure (ICP) in IIH was heightened in the 1990s, with studies of direct venous manometry in IIH patients and studies performed in IIH patients undergoing bariatric surgery. Intracranial and central systemic venography and manometry were performed in 10 patients with increased ICP associated with various disorders (1 congenital stenosis, 2 idiopathic, 5 morbid obesity, 1 tumor compressing the dural sinus, 1 craniodiaphyseal dysplasia, and bony overgrowth of the skull) (9). All patients had CSF pressures above 200 mm H₂O and had no ventriculomegaly. No venous outflow obstruction was found in the obese patients, but some degree of stenosis or occlusion was seen in the other 5 patients (including those with congenital stenosis and tumor). Superior sagittal sinus pressure was elevated in all 7 patients in whom it was measured, including the 5 obese patients. The mean increase was small (1.8 mm Hg above normal) in patients without obstruction, and it is uncertain whether the elevation was statistically significant. Central venous pressure was measured in 6 of the 7 patients who had venous sinus manometry and was abnormal in 5 patients. Patients with venous sinus occlusion were treated with angioplasty/thrombolysis or shunting. The patient with the tumor underwent a CSF diversion procedure (shunt), and the patients with IIH were treated with a combination of shunt, optic nerve sheath fenestration, or gastric stapling. None of the manometric measurements was repeated following treatment.

Numerous studies have demonstrated transverse sinus stenosis (TSS) in patients with IIH. Whether TSS causes IIH or whether IIH causes TSS remains unanswered. MR venography (MRV) and conventional angiography with venous imaging are often normal when a substantial pressure gradient is present. The association between IIH and TSS is quite strong as shown by (high-resolution) autotriggered elliptic-centric ordered (ATECO), 3-dimensional, gadolinium-enhanced MRV (ATECO MRV), which demonstrated transverse dural sinus stenosis in 90% of 29 IIH patients (10) with a high interrater correlation.

King et al (11) studied 9 patients with IIH and 2 patients with minocycline-induced intracranial hypertension by CT, MRI, digital subtraction internal carotid arteriography, and dural sinus venous manometry. Venous pressure was measured in the superior sagittal, left sigmoid, and transverse sinuses. Pullback pressures were measured in the superior sagittal sinus, torcular herophili, proximal and distal transverse sinuses, sigmoid sinuses, and jugular bulbs. Normal controls, however, were not used because the procedures are invasive. All 9 IIH patients had increased pressure in the superior sagittal sinus (14–23 mm Hg; normal = 2–7 mm Hg) and proximal transverse sinus. There was a large (10–20 mm Hg) pressure gradient between the superior sagittal sinus and the...
internal jugular vein in IIH patients. The angiography findings did not always correlate with the manometry findings. A gradually tapered narrowing of the transverse sinus was frequently observed. The authors proposed that a mural thrombosis associated with thrombotic factors related to obesity was the cause of the dural sinus stenosis and pressure gradient. The 2 patients with minocycline-induced intracranial hypertension had normal studies.

The same researchers subsequently performed an elegant study confirming the reciprocal relationship between cerebral venous pressure and CSF pressure (12). Twenty-one patients with confirmed IIH underwent digital subtraction internal and external carotid angiography, dural sinus venography, and manometry. Immediately afterward, 8 of the patients underwent lateral C1-2 puncture and their CSF pressure was recorded before and after 20–25 mL of CSF was removed, after which the cerebral venous pressure measurement was repeated. Control subjects consisted of patients with other diagnoses or those who were suspected of having IIH, but the diagnosis was later proven incorrect. Nineteen of the 21 IIH patients showed a large pressure gradient across the transverse venous sinus. Lowering of the ICP by removal of CSF produced a pressure drop within the transverse sinus between 12 and 41 mm Hg in 6 patients. The pressure drop in the other 2 patients was 4 and 6 mm Hg, respectively; both patients had only a small drop in CSF pressure after the cervical puncture. The drop in pressure in the proximal transverse sinus was most dramatic in patients with the highest pressures before the cervical puncture. Their results correlate nicely with the previous studies showing that at high ICPs, the transverse sinuses could collapse, producing increased superior sagittal sinus pressure. The TSS in such patients resolved after interventions to lower the CSF pressure, such as lumbar puncture or shunting (13,14). Based on these studies, many investigators have concluded that increased venous pressure results from, rather than causes, increased ICP in IIH in most cases (15).

### PRO—Stenting for transverse sinus stenosis in idiopathic intracranial hypertension: Rebekah Ahmed and G. Michael Halmagyi

When maximum medical treatment (e.g., weight loss, acetazolamide, furosemide, and topiramate) fails in IIH, invasive treatments, such as optic nerve sheath fenestration or CSF shunting, are often recommended. Although these can be effective initially, they can also have significant complication and failure rates. The mortality rate of intracranial shunts can be as high as 1% (16), and the morbidity from all CSF shunting procedures (17) includes shunt migration or dislocation, infection, acquired tonsil herniation, and intracerebral hemorrhage (18). In addition, up to 64% of ventriculoperitoneal and lumboperitoneal shunts fail within 6 months and require revision due to recurrence of headache and papilledema (19). Likewise, optic nerve sheath fenestration has a reported surgical complication rate of up to 40% (20), including visual loss, motility and pupillary dysfunction, and vascular complications. Such poor results have been tolerated due to a lack of a viable alternative (21). We propose that stenting a transverse sinus in IIH patients unresponsive to maximal medical therapy, who have stenosis of a dominant transverse sinus or stenosis of both transverse sinuses, is now a viable and effective alternative to CSF shunting procedures.

The first report of TSS stenting in IIH by Higgins et al in 2002 (22) was of an overweight female patient unresponsive to medical treatment, with bilateral TSSs and raised lumbar CSF and cerebral venous sinus pressures. Transverse sinus stenting abolished the pressure gradient across the stenosis and improved the patient’s symptoms and signs. Since then, individual case reports and small case series have appeared (23–25). Higgins et al (26) reported 12 more cases of venous sinus stenting; of whom 5 became asymptomatic, 2 improved, and 5 remained unchanged. However, 5 of their patients had undergone previous CSF diversion procedures, 2 had functioning ventriculoperitoneal shunts at the time of the stent—they did not improve. Our group (27) reported 4 stented IIH cases: headache improved in all 4 and vision improved in 3. Donnet et al (28) reported 10 IIH patients, stented without complication, 6 being “cured” and 4 improved. Bussiere et al (29) reported 10 IIH patients who were stented, with resolution of the venous hypertension in all patients and symptom improvement in most.

We have now stented a further 46 patients with IIH and papilledema, all either unresponsive to maximal medical treatment or with fulminant IIH (30). We have reviewed their clinical, venographic, and ICP data before and after TSS stenting and followed up them for 2 months to 9 years. In these 46 patients, stenting 1 transverse sinus and providing 1 functioning sinus lowered venous pressures and abolished papilledema and accompanying symptoms.

All these patients either had 1 hypoplastic transverse sinus and a stenosis of the other sinus or bilateral TSS. In our experience, the presence of 1 functioning transverse sinus precludes the development of venous hypertension due to stenosis of the other. The mean superior sagittal sinus pressure before stenting was 34 mm Hg, with a mean TSS gradient of 20 mm Hg. Figure 1 shows the gradient across the stenosis vs the sagittal sinus pressure in our patients. The mean lumbar CSF pressure before stenting was 320 mm H2O. In all the 46 patients, stenting immediately abolished the TSS pressure gradient, rapidly improved IIH symptoms, abolished papilledema, and lowered the superior sagittal sinus pressure to a mean of 16 mm Hg (210 mm H2O). In 6 patients, symptom relapse (headache) was associated...
with increased venous pressures and recurrent stenosis adjacent to the previous stent. In these cases, placement of another stent again abolished the TSS pressure gradient and improved symptoms. Of the 46 patients in our series, 43 have been cured of all IIH symptoms. Three have ongoing headaches but normal venous pressures on venography, suggesting another cause for the headaches.

Our complication rate was 11% and included transient unilateral headache, transient unilateral hearing loss in 2 patients, allergic reaction to antiplatelets in 2 patients, an anaphylactic reaction to the anesthetic agent in 1 patient, and the development of subdural and subarachnoid blood during the procedure in 2 patients requiring immediate craniotomy (both patients made a full recovery). One female patient was not included in our study, as she had a functioning ventriculoperitoneal shunt and underwent TSS stenting after 30 previous shunt revisions. Unfortunately, at the end of the procedure, despite a patent stent and venous sinuses, she developed uncontrollable intracranial hypertension and died. An autopsy found that she had died of intracranial hypertension secondary to hypoventilation and the resultant hypercapnia at the end of the anesthesia. We believe that it is likely that this complication would have occurred regardless of the invasive intervention performed if she had been hypoventilated.

Is TSS a cause or an effect of the high ICP in IIH (15)? Since the association of IIH and TSS was shown (11), much has been written about whether the TSS causes (31) or is caused by the IIH (12,14,32,33). With the development of ATECO MRV (34), it is now possible to show the TSS noninvasively and decide whether the stenosis is likely due to intrinsic or extrinsic factors (10). Previously with time-of-flight MRV, a TSS was often interpreted as a flow-related artifact (35). Direct retrograde cerebral venography and manometry allows direct measurement of the venous sinus pressures and the pressure gradient across the stenosis (11). Regardless of whether TSS is the cause or the effect of IIH, we believe that by stenting just 1 transverse sinus and providing a normally functioning sinus, venous pressures are lowered and papilledema resolves in IIH.

We propose that venous hypertension develops in IIH by 1 of 2 mechanisms. In the minority of cases, arachnoid granulations or septal bands (36) swell, causing intrinsic stenosis of the sinus. In the majority of cases, the key feature is the collapsible transverse sinus (a Starling-like resistor), which is vulnerable to extrinsic compression from intracranial hypertension itself. Preventing collapse of the sinus with a rigid wall

![Graph showing pressure gradient across the stenosis vs superior sagittal sinus (SSS) pressure in the 46 patients who underwent TSS stenting.](image1)

**FIG. 1.** Graph showing pressure gradient across the stenosis vs superior sagittal sinus (SSS) pressure in the 46 patients who underwent TSS stenting.

![Mechanism by which stenosis of collapsible transverse venous sinus leads to intracranial hypertension.](image2)

**FIG. 2.** Mechanism by which stenosis of collapsible transverse venous sinus leads to intracranial hypertension.

![Model simulations demonstrating the change in CSF pressures ($P_f$) following infusion and withdrawal of CSF in an IIH patient with a collapsible sinus (A) and then the same patient (using the same rate and volume) with the sinus stented (B). The creation of a rigid sinus by stenting means the patient is no longer alternates between a normal pressure and elevated pressure state, but stays in the normal-pressure state.](image3)

**FIG. 3.** Model simulations demonstrating the change in CSF pressures ($P_f$) following infusion and withdrawal of CSF in an IIH patient with a collapsible sinus (A) and then the same patient (using the same rate and volume) with the sinus stented (B). The creation of a rigid sinus by stenting means the patient is no longer alternates between a normal pressure and elevated pressure state, but stays in the normal-pressure state.
stent is the key to the effectiveness of transverse sinus stenting. A mathematical model (37) predicts that intracranial hypertension compresses a collapsible transverse sinus causing venous flow obstruction, which results in further venous hypertension, which then decreases CSF absorption and causes further increases in ICP, which then feeds back causing further external compression of the transverse sinus and further stenosis (Fig. 2).

In the presence of a collapsible sinus, various perturbations in the model produce a transition from a normal-pressure state to a high-pressure state or vice versa. Such perturbations include an increase in cerebral blood flow, an infusion of CSF (leading to transition from the normal to elevated state), withdrawal of CSF, or reduction in the rate of CSF production (leading to transition from the elevated to normal state). Treatment with acetazolamide (which reduces CSF production) or a CSF shunt (which provides an alternate drainage pathway for CSF) induces transition from a high-pressure to normal-pressure state. Repeated lumbar punctures with the removal of CSF might have a similar effect. In a simulation of the high-pressure state, insertion of a stent, modeled by removing the Starling-like resistor, giving a rigid-walled venous sinus, results in transition to the normal-pressure state (now the only stable state), with further perturbations no longer leading to a high-pressure state (Fig. 3).

It has been proposed that prior to stenting, the MRV should be repeated after lumbar puncture and CSF removal, to see if the stenosis resolves. This would suggest a reversible high ICP-related stenosis (32). We have done this in several patients and have found that after several weeks, once the ICP rises again and the effects of the CSF removal from the lumbar puncture “wear off” the stenosis returns. In our opinion, to perform repeated lumbar punctures and venous imaging (especially CT) is neither practical nor cost-effective. It does not matter if the stenosis is the “chicken or the egg” (15). By stenting the collapsible transverse sinus, patients no longer flip between a normal-pressure state and high-pressure state but instead remain in the normal-pressure state. We have found that further lumbar punctures and medications are not required after stenting the transverse sinus.

Regardless of whether TSS is the cause or effect of IIH, some patients require additional treatment, other than optic nerve sheath fenestration, subtemporal decompression, or CSF shunting, in order to save vision and/or control intractable headache. We believe that transverse sinus stenting is such a treatment. In our study, although 13% required a repeat stent, this is a significantly lower rate than the current failure rate of CSF shunting. We propose that patients with IIH being considered for CSF shunting or optic nerve sheath fenestration should undergo an MR venogram (using the ATECO technique) or a CT venogram. If this study suggests TSS, then we recommend cerebral venography with manometry and consideration for transverse sinus stenting.

CON—Stenting of the transverse sinuses is not a reasonable treatment for most patients with idiopathic intracranial hypertension: Deborah I. Friedman

Stenting in IIH

To date, the data regarding stenting for IIH have only come from a small and uncontrolled case series of selected patients. There have been no randomized trials with a control group or sham stenting. Various authors attribute the lack of such a control group to the invasive nature of the procedure, but there are clinical trial designs that could overcome this argument. The various series (n = 8 with 31 patients) were reviewed in detail by Arac et al (38), who added 1 additional patient. This series now will be summarized.

Venous sinus stenting was performed on 12 cases of IIH (26). All patients had intractable headaches and a visual disturbance lasting 5 months to 12 years. Two patients had severe visual loss and 8 had chronic papilledema. All had previously received medical treatment, optic nerve sheath fenestration, or a shunt procedure. No surgery had been performed within 10 months of stenting. Carotid angiography, cerebral venography, and manometry were performed on all patients. Stenting was done under general anesthesia. Ten patients underwent unilateral sinus stenting only and 2 underwent contralateral stent placement later. At follow-up, 5 patients were asymptomatic, 2 had improved except for residual headache, and 5 were unchanged. Papilledema resolved in 4 patients and improved in 1. Two patients received thrombolytic treatment successfully in the immediate postprocedural period for an intraluminal thrombus. Venography after stenting showed a reduction in intrasinus pressure that did not necessarily correlate with clinical improvement.

The same authors reported the results of stenting in an additional 8 patients with IIH (39). The duration of disease and previous treatment were not indicated in the report. All had papilledema prior to stenting that resolved after the procedure. Seven patients had headaches over the stenting site that resolved in days to weeks. Six of 7 had long-term improvement in vision that was dramatic in 1 case (light perception to almost normal vision within weeks). Another had resolution of bilateral abducens palsies.

Nine consecutive patients at another center were evaluated with direct retrograde cerebral venography and manometry with simultaneous CSF pressure measurement in 2 patients (27). All patients had been previously treated with various modalities, including acetazolamide (3 patients), optic nerve sheath fenestration (3 patients), shunt (6 patients, 5 of whom had numerous revisions), and subtemporal decompression (1 patient). Five patients had partial transverse sinus obstruction and 4 were treated with stents. One
patient with complex venous anatomy was not stented but had a shunt placed with a successful outcome. Four patients were feeling well and required no additional treatment. The authors postulated that IIH may be caused by dural venous sinus thrombosis in some patients and cause venous stenosis in others. Donnet et al (28) reported their experience with stenting in 10 patients with “refractory” IIH. “Refractory” in this series was defined as lack of response to acetazolamide (dose not specified), which would hardly be considered refractory by most neuro-ophthalmologists treating IIH.

While these reports are encouraging, complications of stenting reported in the literature include headache, transient hearing loss, transient unsteadiness, and a life-threatening acute subdural hematoma (39). The subdural hematoma developed during venography and stenting in a patient who also had an optic nerve sheath fenestration and external ventricular drainage. I am personally aware of another patient who suffered a life-threatening subdural hematoma requiring a ventriculostomy and craniectomy following an unsuccessful stenting procedure. Venous re-stenosis has also occurred.

An update from the Sydney Group reported above, having the most experience worldwide performing TSS stenting for IIH, was presented at the 2011 annual meetings of the North American Neuro-Ophthalmology Society (February 2011) and the American Academy of Neurology (April 2011) (personal communications) (40). These 46 patients had symptomatic improvement within hours in most patients, resolution of papilledema in all patients over weeks, and persisting improvement in visual symptoms and visual fields in 43 patients. Six patients had a relapse with recurrent stenosis adjacent to the previous stent. These patients underwent placement of another stent with improvement. The most troubling aspect of their stenting experience was the complications. “Minor” complications included anaphylaxis and hearing loss. “Major” complications included subarachnoid hemorrhage and subdural hematoma. One patient with a mural thrombus developed a subdural hematoma after urokinase treatment. There was death in a patient with uncontrollable cerebral edema following the procedure that was attributed to anesthetic technique. The overall safety profile of the procedure is difficult to ascertain, largely because of publication bias as there is an unknown number of poor stent outcomes that likely have not been published. Although there is a small but real mortality risk with CSF shunting procedures, to my knowledge, there have not been any deaths associated with an optic nerve sheath fenestration. It would be difficult to recommend stenting and its associated morbidity and mortality if the indication is visual loss and optic nerve sheath fenestration is easily available.

It is difficult to interpret the findings of various reports, as the criteria for stenting are variable between centers and “treatment failure” is poorly defined. Surgical intervention for IIH is generally reserved for patients with visual loss. Optic nerve sheath fenestration may improve headaches in some cases but is not used for the treatment of headache alone. Although shunting is often considered the “definitive” treatment for IIH-associated headaches, large case series suggest otherwise. The long-term efficacy of shunting for headache control is poor (41,42). Chronic headache as a measure of treatment failure is an imprecise criterion for stenting. The details of headache treatments used in the Sydney group’s patients are not provided, and all invasive treatments for headache tend to have a good success rate. There is a high placebo response rate in all studies of treatments used for headache disorders, particularly for migraine. Resolution of papilledema is an important and objective outcome measure, although the headache severity in IIH does not correlate with the degree of papilledema. Stenting patients with mild disease may offer no benefit— and much greater risk—than maximal medical therapy.

Although there is biologically plausible rationale for stenting in selected patients with IIH and TSS, there is no randomized controlled clinical trial evidence to document efficacy. However, patients sometimes fail to improve with conventional therapy, and no currently used treatment is particularly helpful in those with fulminant IIH. One may consider stenting in IIH only when the following conditions are met: 1) The procedure is performed by an interventionalist with experience in venous sinus angiography and stenting, in a facility with neurosurgicalbackup available in case of a neurologic emergency or complication, 2) potential candidates are screened for reversibility of the venous sinus stenosis upon lowering of the CSF pressure prior to considering stenting, 3) conventional treatments, including medical therapy and surgical therapy (e.g., shunt, optic nerve sheath fenestration) are tried without success, 4) the patient’s vision continues to deteriorate despite ongoing conventional therapy. The rate of serious complications is worrisome, particularly when compared to existing treatments.

Even if dural venous blockage is a cause or the only cause of IIH, larger clinical studies of stenting must demonstrate the long-term safety and efficacy of this procedure before it can be adopted for IIH cases refractory to standard treatment methods. Because standard medical treatment is generally successful and much less invasive, stenting should not be adopted until such measures have failed.

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**Rebuttal: Rebekah Ahmed and G. Michael Halmagyi**

The main argument presented against TSS stenting in IIH is the lack of a randomized controlled trial to document its efficacy and complication rate, yet there is also no randomized controlled data to document the efficacy of
We agree that stenting should only be performed by an experienced neurointerventionalist, just as optic nerve sheath fenestration should only be done by a surgeon experienced with the procedure. We do not agree that stenting should only be tried once shunting and optic nerve sheath fenestration have failed. In our opinion, this only results in patients undergoing additional unnecessary procedures.

Patients who have failed maximal medical management for treatment of IIH and are being considered for shunt placement or optic nerve sheath fenestration should also undergo MRV (ATECO technique) and cerebral venography and manometry to see if they are candidates for stenting. Even if the stenosis disappears with the lowering of ICP and recurs with high ICP, these patients should be considered for stenting. We consider stenting to be like democracy; it might not be perfect, but it is better than the alternatives.

There is no comparison between transient diplopia or a worsening visual field defect after optic nerve sheath fenestration and a subdural hematoma with brain herniation, even if the patient recovers. Despite the small number of patients who experience this devastating complication, the morbidity and expense of intensive care and additional neurosurgical treatments needed to save these patients are not trivial. Moreover, while optic nerve sheath fenestration is not offered at all centers, the availability of neurointerventionalists who have experience with stenting is also limited.

My only direct experience with the democratic process in the United States does not support the contention that choosing a candidate who is “better than the alternative” leads to a good outcome. Although there is much political influence in medicine, medicine is not politics and we try to use scientifically based evidence to make thoughtful treatment decisions. Primum non nocere.

**Summary: Andrew G. Lee and Valérie Biousse**

Although venous stenoses play some role in IIH, much remains to be understood before supporting routine endovascular stenting of stenosed intracranial venous sinuses in patients with IIH. Pilot data have opened the door to a completely new type of treatment, whose indications, efficacy, and safety remain insufficient at this point. A recently launched prospective pilot study evaluating venous stenting in IIH will hopefully provide more insight into this new treatment (43).

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Neuro-Ophthalmology and Pregnancy: What Does a Neuro-Ophthalmologist Need to Know?
Kathleen B. Digre, MD

Abstract: Management of the pregnant woman with a neuro-ophthalmic disorder may be challenging. Physiologic changes in pregnancy make vascular conditions more frequent, including retinal artery occlusion, spontaneous orbital hemorrhage, and pituitary apoplexy. Papilledema may signal cerebral venous sinus thrombosis or idiopathic intracranial hypertension. Manifestations of severe pre-eclampsia and eclampsia include choroidal infarction, serous retinal detachment, and disorders of higher cortical function, such as alexia, simultanagnosia, and cerebral blindness. Cranial neuropathies have also been reported. Transient Horner syndrome, intracranial hypotension with concomitant esotropia may occur in the postpartum period. Treatment of the neuro-ophthalmic complications of pregnancy requires an understanding of the risks of medications. Taking optimal care of the mother will usually result in the best care for her baby.

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Pregnancy, a unique condition in clinical medicine, involves simultaneous treatment of both the woman and her fetus(es). When a pregnant woman has a neuro-ophthalmic problem, many neuro-ophthalmologists hesitate about diagnostic studies and therapeutic interventions. My interest in this subject began during my fellowship at the University of Iowa— in part, thanks to my husband, a high-risk obstetrician. My fellowship project was examining pregnant women with severe preeclampsia and eclampsia for neurologic and neuro-ophthalmologic findings. My colleague, Dan Jacobson, shared my interest, and together we published a case of spontaneous orbital hemorrhage (1). Dan went on to report a cranial neuropathy occurring in pregnancy (2) and to become a masterful clinician, teacher, and writer. Our mutual interest in neuro-ophthalmic complications in pregnancy inspired my Jacobson Lecture.

Here, I review normal changes in pregnancy, which can affect the eye and brain. I also describe evaluation of neuro-ophthalmic conditions in pregnancy, and I discuss common problems, including vascular complications, papilledema, eclampsia, cranial neuropathy, and postpartum neuro-ophthalmic events.

WHAT ARE THE NORMAL CHANGES IN PREGNANCY THAT COULD AFFECT THE EYE OR BRAIN?

All physiologic changes in pregnancy are mediated by the fetus and placenta and are designed to optimize development in utero and facilitate a safe birth. Blood volume and cardiac output are increased by 30%–50% at term in order to adequately perfuse mother’s uterus (and fetus). An increase in extracellular fluid (approximately 2 L by term) results from a decrease in serum osmolality (3). In anticipation of controlling blood loss during delivery, plasminogen, fibrinogen, and factors I, V, VII, IX, and X are increased...
while fibrinolysis is decreased. Smooth muscle hyperplasia helps accommodate the enlarging uterus, and fragmentation of reticular fibers within blood vessel walls occurs, resulting in an increased risk for vascular complications (4).

Immunologic changes in pregnancy, primarily in cellular immune function, occur because the fetus is immunologically distinct from its mother (5,6). Many immune-mediated problems, like rheumatoid arthritis and ankylosing spondylitis, can improve in pregnancy. In the postpartum state, immunologic problems may worsen. For example, women with multiple sclerosis are more likely to have a demyelinating attack postpartum (7,8).

Although normal human pregnancy is approximately 38–40 weeks in duration, approximately 12% of births in the United States occur more than 3 weeks before the due date. While three-quarters of these are “late preterm” (34–36 weeks) and have relatively few complications, approximately 3% are less than 34 weeks and are at an increased risk for perinatal and long-term morbidity and mortality. Most obstetricians and neonatologists predict rapidly improving survival rates for babies born at or beyond 24 weeks (9). Treatment and intervention decisions during pregnancy must always consider the fetal risks from continued in utero residence versus delivery.

CHANGES IN THE EYE IN PREGNANCY

Excellent reviews summarize normal changes in the eye and ophthalmic complications (10–13). Pregnant women report refractive changes, thought to be partially due to progesterone-mediated changes in corneal fluid content. These same fluid shifts may contribute to the common complaint of blurred vision and poorly fitting contact lenses during pregnancy (14,15). A myopic shift of less than 1 diopter often occurs (16). Myopia-related reduction in night vision can happen; if it is pronounced, the clinician should consider vitamin A deficiency. Intraocular pressure decreases during pregnancy (17). The cause is attributed to reduced episcleral venous pressure, greater aqueous outflow, and effects of progesterone. There are no known retinal or optic nerve changes in normal pregnancy.

NEUROLOGIC CHANGES IN PREGNANCY

The Brain

Volumetric MRI techniques have shown that the brain becomes somewhat smaller and the ventricles slightly larger. These changes may be related to alkalosis and hormones. Brain volume decrease seems to reverse itself postpartum (18,19). Biochemical and hormonal changes in the brain during and after pregnancy prepare a woman for motherhood (20). Prolactin levels are increased, and cerebrospinal fluid (CSF) prolactin is elevated. Prolactin may have an effect on maternal-newborn bonding and feeding (21).

The pituitary gland increases in size approximately 0.08 mm/week, its weight increases 30%, and its volume increases 2-fold. The pituitary gland often appears enlarged on MRI and returns to normal approximately 1–2 weeks postpartum, whether the woman is nursing or not (22). While normal enlargement rarely causes problems, chiasmal compression has been reported (23).

Sleep changes occur in all trimesters. Disrupted sleep breathing is associated with rates of pre eclampsia, endothelial damage, and fetal abnormalities (24,25). Pregnancy and the puerperium are stressful life events, and hormonal and biochemical changes increase the frequency of mood changes. Depression occurs within the first week of delivery in 50–70% of pregnancies. In 10–20%, it is serious and requires attention (26).

Cerebrospinal Fluid Pressure in Pregnancy

A pregnant woman has an average normal CSF pressure of 12.7 mm Hg (27) or 167 mm CSF. While 250–300 mL of blood is transfused into the vascular circulation with each contraction, there is no increase in intracranial pressure during a contraction alone. It has been shown that CSF pressure increases during labor, due to muscular contraction in response to pain (28–31). Women can increase pressures to more than 700 mm CSF with Valsalva maneuver (32).

EVALUATING A NEURO-OPHTHALMIC PROBLEM IN PREGNANCY

Evaluation should proceed as it would if the woman were not pregnant. We should assume that if we diagnose the mother correctly and treat her appropriately, she will adequately care for the fetus. We use the same tools as we would to make any diagnosis in neuro-ophthalmology (Table 1).

MEDICATIONS IN PREGNANCY

No studies have prospectively evaluated medication safety in pregnancy. Much of what we know is derived from animal studies and toxicity reports. The major classification of drugs in pregnancy is from the Food and Drug Agency (FDA) classification (Table 2).

VASCULAR DISORDER IN PREGNANCY

Cerebral Stroke and Retinal Vascular Disorders

It used to be thought that pregnancy alone increases the risk of cerebrovascular disease by 3–13 times the expected rate in healthy young women, and it still does in some countries (35). The risk of stroke during a normal healthy pregnancy is approximately 0.7, but stroke risk is definitely increased postpartum to 8.7 (95% confidence interval, 4.6–16.7) (36). Cerebrovascular disease accounts for 0.47%–6% of maternal mortality (37). Retinal vascular events occur; it is important to diagnose their cause. In some cases, simple
aspirin (FDA class C) is prescribed; in others, prophylactic anticoagulation with heparin or heparinoids (FDA class B) is indicated. Warfarin (FDA class X) generally is avoided because of associated fetal malformations and abnormalities resulting from concurrent fetal anticoagulation (38).

Embolism from a cardiac source is the most common cause of an acute vascular event in this age group (Table 3). Conditions to consider include rheumatic heart disease, endocarditis (bacterial and nonbacterial), and paradoxical embolism (often worsened by venous stasis in the lower extremities and an undetected patent foramen ovale) (39). Peripartum cardiomyopathy, an uncommon disorder, is poorly understood and causes acute heart failure that may not be reversible. These women often first present with symptoms weeks or months postpartum (40). Amniotic fluid embolism is a catastrophic event with often multiple arterial occlusions and is fortunately a rare cause of retinal or cerebral artery occlusion (41). Evaluation of vascular embolic disorders should proceed as if the woman were not pregnant. Besides evaluation of a cardiac source, consider hematologic disorders, such as lupus anticoagulant, protein C deficiency, and prothrombin 20210.

TABLE 1. Diagnostic procedures in neuro-ophthalmology

<table>
<thead>
<tr>
<th>Test</th>
<th>Risk to Mother</th>
<th>Risk to Fetus</th>
<th>Contraindication</th>
<th>Notes</th>
</tr>
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<tr>
<td>MRI</td>
<td>None</td>
<td>None known</td>
<td>Metal in mother</td>
<td>Gadolinium is FDA class C</td>
</tr>
<tr>
<td>CT</td>
<td>None</td>
<td>Minimal</td>
<td>Dye allergy</td>
<td>Shield the abdomen; iodinated contrast dye class B</td>
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<tr>
<td>Angiogram</td>
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<td>Minimal</td>
<td>Dye allergy</td>
<td>Shield the abdomen</td>
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<tr>
<td>Lumbar puncture</td>
<td>None</td>
<td>None</td>
<td>Incipient herniation in the mother</td>
<td>—</td>
</tr>
<tr>
<td>Fluorescein angiogram (FDA class C)</td>
<td>None</td>
<td>None known</td>
<td>Allergy</td>
<td>Crosses placenta and also into breast milk (33,34)</td>
</tr>
<tr>
<td>Indocyanine green angiography (FDA class C)</td>
<td>None</td>
<td>None known</td>
<td>Dye allergy</td>
<td>Does NOT cross placenta; used in pregnancy (33)</td>
</tr>
<tr>
<td>Dilating drops tropicamide (FDA class C)</td>
<td>None</td>
<td>None known</td>
<td>Angle-closure glaucoma</td>
<td>Occlude puncta when administering</td>
</tr>
</tbody>
</table>

TABLE 2. FDA classification

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A:</td>
<td>Controlled studies show no risk.</td>
</tr>
<tr>
<td>B:</td>
<td>Animal studies show risk but no evidence of risk is apparent in humans.</td>
</tr>
<tr>
<td>C:</td>
<td>Risk is unknown but cannot be ruled out (the classification of most drugs).</td>
</tr>
<tr>
<td>D:</td>
<td>Studies in animals or humans show risk, but the benefit may outweigh the risk in some instances, distinctly.</td>
</tr>
<tr>
<td>X:</td>
<td>Studies in animals or humans show fetal risk, which clearly outweighs any possible benefit. Do not prescribe “X” drugs.</td>
</tr>
</tbody>
</table>

Orbital Varix

Orbital varix usually presents with a slowly progressive sense of fullness around the eye. Sometimes bending over increases the fullness. Orbital ultrasound, CT, or MRI are appropriate diagnostic studies. The varix may become symptomatic due to increased blood volume. Little is known about the management (46). Complications resemble those observed in women who are not pregnant: hemorrhage, glaucoma, and thrombosis. Cesarean section is not mandatory; labor can be managed with an epidural and “rest and descent,” with assisted vaginal delivery with vacuum or forceps.

Vascular Events of Pituitary Gland: Sheehan Syndrome or Pituitary Apoplexy

Pituitary apoplexy presents either with lack of menstruation after pregnancy or more dramatically with the sudden onset of severe headache, vomiting, and altered mental status. The diagnosis is made by MRI, CT, or angiogram. Treatment is usually unnecessary since the hemorrhage generally resolves spontaneously.

TABLE 3. Causes of acute ischemic central or branch retinal arterial occlusions and other arterial vascular events in pregnancy

| Embolic (cardiac)                          |                  |
| Arterial occlusive (thrombotic)            |                  |
| Hypercoaguable state                       |                  |
| Amniotic fluid embolism                    |                  |
| Drug use/abuse (cocaine, ephedrine)        |                  |
| Hypotension                               |                  |
| Arteritis (especially with systemic lupus) |                  |
| Susac syndrome (42)                        |                  |
| Hematologic disorders: thrombocytopenic purpura, sickle cell disease, protein C and S, anti-thrombin III, Leiden factor V, lupus anticoagulant |                  |

See also Digre and Varner (43), which lists causes of stroke and vascular disorders.
of a headache and variable visual loss. There are 2 instances where apoplexy can occur: 1) hemorrhage into an unsuspected pituitary tumor during or after pregnancy and 2) after sudden and large hemorrhage or blood volume loss. While most cases present postpartum, looking for this entity under the appropriate circumstances can be important (47,48). Treatment of pituitary apoplexy may be surgical, if vision or life is threatened, or hormone replacement (49,50).

**PAPILLEDEMA IN PREGNANCY**

Papilledema discovered in pregnancy poses significant challenges (51). Increased intracranial pressure may be primary (idiopathic intracranial hypertension [IIH]) or secondary (mass lesion, cerebral venous thrombosis, meningitis, eclampsia). MRI and magnetic resonance venography or CT venography is required to rule out cerebral venous sinus thrombosis, a long-recognized cause of stroke in pregnancy. Incidence of cerebral venous sinus thrombosis in pregnant women is between 1/1000 and 1/10,000. Symptoms may be indistinguishable from those of IIH (52). However, more serious neurologic complications may occur, including seizures and hemiplegia (53). Possible etiologies are outlined in Table 4. Leiden factor V (protein C resistance) is increased 8-fold. Other genetic factors, such as protein C and S deficiencies, prothrombin gene, and homocysteinemia, may be symptomatic. Women are more prone to autoimmune diseases, which could promote venous sinus thrombosis, such as anticardiolipin antibodies or systemic lupus erythematosus. While venous sinus thrombosis most commonly occurs postpartum, it can take place during pregnancy.

Cerebral venous thrombosis must be treated. Pregnant women who received heparin had 50% fewer deaths than those not anticoagulated (54,55), with no increase in maternal or perinatal complications. Enoxaparin (FDA class B) is used frequently rather than heparin (FDA class B) because of the ease of administration and lower complication rate. Warfarin (FDA class X) is not used during pregnancy because of possible fetal posthemorrhagic malformations; however, it can be used postpartum including during lactation. Women with papilledema from venous sinus thrombosis should be followed like individuals with IIH (see below).

IIH commonly is seen in women of childbearing age. The use of acetazolamide in pregnancy has not been systematically studied. This is an FDA class C drug, and no evidence of teratogenicity has been reported (56). Because fetal structural development is essentially complete by the end of the first trimester, concerns about teratogenesis are generally nonissues later in pregnancy. Other diuretics could be considered: chlorthalidone (FDA class B), furosemide (FDA class C), or hydrochlorothiazide (FDA class B). Other treatments include limitation of weight gain (57). If vision is threatened, simple CSF drainage may temporize the situation. Optic nerve sheath fenestration should be considered. Lumbar-peritoneal and ventricular peritoneal shunts may be challenging (51,58–61).

Because 50% of pregnancies in the United States are unplanned, preconceptional counseling is encouraged whenever IIH diagnosis is established in a woman of reproductive age. Weight control before and during pregnancy may be helpful.

Headache management of IIH in pregnancy is challenging. Early on, nonsteroidal anti-inflammatories are FDA class B; later, they become FDA class C because of the possible risk of premature closure of the ductus arteriosus and decreased fetal renal perfusion. Optimal treatment is usually a diuretic, such as acetazolamide, and a migraine headache preventative (β-blockers, calcium channel blockers, tricyclic antidepressants, rarely anticonvulsants—all FDA class C or D) (62).

**TABLE 4. Etiologies of venous thrombosis in pregnancy and the puerperium**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C and S</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
</tr>
<tr>
<td>Leiden Factor V (protein C resistance)</td>
</tr>
<tr>
<td>Prothrombin gene</td>
</tr>
<tr>
<td>Homocysteinemia</td>
</tr>
<tr>
<td>Paraproteinemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
</tr>
<tr>
<td>Systemic lupus; Crohn disease</td>
</tr>
<tr>
<td>Behcet disease</td>
</tr>
<tr>
<td>Middle ear infection</td>
</tr>
<tr>
<td>Sarcoid</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Postpartum state</td>
</tr>
<tr>
<td>Venous obstruction by meningioma</td>
</tr>
</tbody>
</table>

**PREGNANCY-SPECIFIC NEURO-OPHTHALMOLOGIC CONDITIONS:**

**SEVERE PREECLAMPSIA AND ECLAMPSIA**

The hallmarks for these pregnancy-specific conditions are hypertension and proteinuria, with initial onset in the second half of pregnancy. Preeclampsia is diagnosed with persistent blood pressures above 140/90 mm Hg and greater than 300 mg proteinuria/24 hours. Signs of severe preeclampsia that mandate delivery include blood pressure > 160/110 mm Hg, proteinuria > 5 g/24 hours, and oliguria (<500 mL/24 hour). Other signs and symptoms include persistent visual disturbances, pulmonary edema, congestive heart failure, thrombocytopenia (<100,000/mm³) and elevated liver function tests. The HELLP syndrome (Hemolysis, Elevated Liver function tests, Low Platelets) frequently accompanies the condition.

Eclampsia is defined by the development of convulsions and/or coma in a previously preeclamptic woman. Other conditions can be confused with severe preeclampsia or eclampsia, including venous thrombosis, systemic lupus erythematosus, thrombocytopenic purpura, arterial occlusion, drug abuse,
idiopathic seizures, hyponatremia, reversible cerebrovascular constriction syndrome, and Wernicke encephalopathy (especially after hyperemesis gravidum) (63).

I have studied the neuro-ophthalmic findings in severe preeclampsia and eclampsia. In 31 patients, “spots” were reported in 11 patients, color defects in 8, blurred vision in 2, headaches in 19, and visual acuity changes in 2. Others have reported similar findings (64). Funduscopic changes in severe preeclampsia and eclampsia include vascular narrowing, segmental retinal artery vasospasm, or occlusion.

Amsler grid abnormalities strongly predicted retinal vascular changes. In addition, MRI was more likely to be abnormal if the Amsler grid was abnormal. The choroid is frequently affected with choroidal infarctions leading to retinal pigmented epithelial changes and serous retinal detachments due to choroidal effusion (65). The optic nerve may be swollen due to intracranial hypertension, systemic hypertension, or anterior ischemic optic neuropathy (66).

MRI findings in severe preeclampsia and eclampsia are characterized by disruptions at the gray white interface in the parieto-occipital region and the basal ganglia. Diffusion-weighted imaging may show an increased signal in the occipital lobes and in corresponding apparent diffusion weighted imaging may show an increased signal in the parieto-occipital region and characterized by disruptions at the gray white interface. Disseminated hemorrhage involves the posterior visual pathways (75).

Factors that may contribute to the vasogenic edema include increased intracranial pressure, decreased cerebral perfusion, and decreased cerebral autoregulation. There is differential innervation of the posterior visual pathways (76,77). Cerebral autoregulation remains unknown, one theory involves breakdown of cerebral autoregulation. There is differential innervation of the anterior and posterior circulations. Loss of autoregulation in the posterior circulation would explain involvement of the posterior visual pathways (75–79).

The entire slide presentation is available in NOVEL (http://NOVEL.utah.edu/NAM). Also, this presentation can be seen from the NANOS Annual Meeting (2011 Jacobson Lecture) on NOVEL (http://NOVEL.utah.edu/NAM).

**CRANIAL NEUROPATHY**

Cranial neuropathies can occur in pregnancy. The most common is facial neuropathy or Bell palsy followed by sixth and fourth involvement (88). Incidence of Bell palsy is 50 in 100,000; more than two third of these are reported in the third trimester (88,89). The etiology of cranial neuropathy is thought to be an increase in interstitial fluid around the nerve, creating compression. The prognosis is usually good; treatment with prednisone generally is not necessary. Jacobson reported a woman with a superior oblique palsy manifested in pregnancy, with excellent recovery (2).

**POSTPARTUM COMPLICATIONS**

Horner syndrome has been reported following epidural analgesia. It is usually a transient self-limited condition often associated with a high epidural block (90).

Acquired Chiari I malformation has also been reported due to intracranial hypotension, intracranial hypovolemia, or following epidural analgesia with a CSF leak (90). The patient presents with chronic headaches and diplopia often due to a comitant esotropia. Typical findings of intracranial hypotension on MRI can be seen, with low-lying tonsils, flattening of the pons against the clivus, low-lying cerebellum, somewhat enlarged pituitary gland, and gadolinium enhancement of the meninges.

The most important lesson for the neuro-ophthalmologist caring for a pregnant woman is to make the correct diagnosis, using whatever tests are needed. Consider pregnancy-related conditions such as eclampsia and severe preeclampsia and know how to treat them. Finally, remember that what is best for the mother generally will be best for her baby.

The entire slide presentation is available in NOVEL (http://NOVEL.utah.edu/jno). Also, this presentation can be seen from the NANOS Annual Meeting (2011 Jacobson Lecture) on NOVEL (http://NOVEL.utah.edu/NAM).

**ACKNOWLEDGMENTS**

The author thanks Susan Schulman for her expert editorial assistance and Michael Varner for his suggestions.

**REFERENCES**


Literature Commentary


Objective: To assess the recovery process in patients after an acute optic neuritis (ON) attack, comparing static and dynamic visual functions.

Methods: In this prospective controlled study, 21 patients with unilateral first-ever ON were followed over the course of 1 year. Standard visual tests, visual evoked potentials, and optical coherence tomography were assessed repeatedly. In addition, we developed a novel set of motion perceptual tasks to test dynamic visual deficits. fMRI examinations were performed to study the neuronal correlates for the behavioral findings.

Results: Four months after the acute phase, the affected eyes had returned to normal performance levels in the routine visual testing. However, motion perception remained impaired throughout the 12-month period. In agreement with the clinical findings, fMRI studies showed recovery in cortical activation during static object recognition, as opposed to sustained deficit in tasks that require motion perception.

Conclusions: Sustained motion perception deficit following ON may explain the continued visual complaints of patients long after the recovery of visual acuity. Cortical activation patterns suggest that if plastic processes in higher visual regions contribute to the recovery of vision, this may be limited to static visual functions. Alternatively, cortical activation may reflect the visual percept (intact for visual acuity and impaired for motion perception), rather than demonstrating plastic processes. We suggest that motion perception should be included in the routine ophthalmologic tests following ON.

The authors prospectively and longitudinally evaluated multiple static (acuity, visual field, contrast sensitivity), dynamic (motion detection, identification of moving objects), and functional (VEP, functional MRI) tests among patients with a first attack of unilateral optic neuritis. Overall, they found that the static tests returned to normal at 4-month follow-up. The dynamic and functional tests remained abnormal compared to fellow eyes and control eyes for more than a year.

We know from the Optic Neuritis Treatment Trial that treatment with intravenous Solu-Medrol does not affect the final visual outcome with regard to visual acuity and visual field. Many minimalists in our specialty point to this as support for doing nothing for patients with optic neuritis. This study makes me wonder if intravenous corticosteroid therapy would affect recovery of motion detection or not. I do not know if any of these patients were treated or not. Finally, this article can also help manage expectations of patients with an acute optic neuritis.

—Michael S. Lee, MD

This is an interesting article demonstrating persistent deficits in motion perception after final recovery in optic neuritis, even in those with complete recovery of contrast sensitivity. It would be helpful to know if there is a correlation of these test findings with patients’ symptoms. As another feature that doesn’t fully recover, motion perception will be an excellent parameter to measure in clinical trials of medications for MS or optic neuritis.

—Mark L. Moster, MD


Background: Plasma exchange (PLEX) is a beneficial rescue therapy for acute, steroid-refractory, central nervous system inflammatory demyelinating disease (CNS-IDD). Despite the approximately 45% PLEX response rate reported among patients with CNS-IDD, determinants of interindividual differences in PLEX response are not well characterized.

Objective: To perform an exploratory analysis of clinical, radiographic, and serological features associated with beneficial PLEX response.

Design: Historical cohort study.

Setting: Neurology practice, Mayo Clinic College of Medicine, Rochester, MN.

Patients: All Mayo Clinic patients treated with PLEX between January 5, 1999, and November 12, 2007, for a steroid-refractory CNS-IDD attack.

Main Outcome Measure: The PLEX response in attack-related, targeted neurological deficit(s) assessed within the 6-month period following PLEX.

Results: We identified 153 patients treated with PLEX for a steroid-refractory CNS-IDD, of whom 90 (59%) exhibited moderate to marked functional neurological improvement within 6 months following the treatment. Pre-PLEX clinical features associated with a beneficial PLEX response were shorter disease duration (P = 0.02) and preserved deep tendon reflexes (P = 0.001); post-PLEX variables included a diagnosis of relapsing-remitting multiple sclerosis (P = 0.008) and a lower Expanded Disability Status Scale score.
(P = 0.001) at the last follow-up. Plasma exchange was less effective for patients with multiple sclerosis who subsequently developed a progressive disease course (P = 0.046). Radiographic features associated with a beneficial PLEX response were the presence of ring-enhancing lesions (odds ratio = 4.00; P = 0.03) and/or mass effect (odds ratio = 3.00; P = 0.02). No association was found between neuromyelitis optica-IgG serostatus and PLEX response.

**Conclusions:** We have identified clinical and radiographic features that may aid in identifying patients with fulminant, steroid-refractory, CNS-IDD attacks who are more likely to respond to PLEX.

Studies have demonstrated improvement in neurologic function in patients with CNS demyelinating episodes without spontaneous recovery who received plasma exchange (PLEX). In prior reports, features associated with a beneficial response to PLEX included early initiation of treatment, preserved deep tendon reflexes (DTRs), and male sex. It has been proposed that PLEX might work by removing inflammatory and humoral factors contributing to reversible conduction block, prior to permanent axonal damage.

The current study, which is the largest to date, found a slightly different set of features associated with moderate to marked improvement, namely, shorter disease duration, preserved DTRs, a lower EDSS score, a relapsing-remitting course, and MRI with ring-enhancing lesions or mass effect.

This study included patients with MS or NMO and because it included varied types of demyelinating episode, it is hard to glean detailed information about optic neuritis. However, 14% of patients are listed as having optic neuritis, with approximately 35%–40% with moderate to marked improvement, somewhat less than the overall 59% improvement rate. There was similar improvement in a group of patients listed with “visual field defects.” In patients with an NMO-type presentation (34 patients), there was no statistical difference in response between NMO seronegative (83%) and seropositive (68%) status.

The median time from index event to treatment in this study was 23 days (range, 0–186). Such early treatment raises criticism that the beneficial outcome may merely be spontaneous recovery. However, in contrast to findings of prior studies, the benefits were similar for patients treated within 20 days (60%), 21–60 days (60%), and >60 days (55%).

This study is important, and I hope it will encourage further study of PLEX for optic neuritis with suboptimal outcome. While PLEX is commonly employed for NMO patients, it is not frequently used in non-NMO demyelinating optic neuritis. We are likely missing a window of opportunity to improve vision in some of these patients with PLEX in the first few months. With increasing ability to predict nonrecovery (e.g., early RNFL thinning) in optic neuritis than with other demyelinating presentations, we may be able to identify which patients may benefit most from PLEX.

—Mark L. Moster, MD

There just is not enough detail in this article to determine the effectiveness of PLEX in optic neuritis. It is hard to know how many of these “optic neuritis” were NMO patients or MS patients or CIS patients.

Mark, I agree with you that there may be more effective treatments for optic neuritis than observation or intravenous corticosteroids. Perhaps, a pilot study of PLEX in optic neuritis utilizing RNFL and motion detection as outcome measures may be in order. However, with the rising cost of medical care and the generally good visual recovery of patients with optic neuritis, it would be wise to evaluate the cost effectiveness.

—Michael S. Lee, MD


**Purpose:** To examine the biomechanical deformation of load-bearing structures of the optic nerve head (ONH) resulting from raised intracranial pressure, using high-definition optical coherence tomography (HD-OCT). We postulate that elevated intracranial pressure induces forces in the retrolaminar subarachnoid space that can deform ONH structures, particularly the peripapillary Bruch membrane (BM) and retinal pigmented epithelial (RPE) layers.

**Methods:** We compared HD-OCT optic nerve and peripapillary retinal nerve fiber layer (RNFL) findings in eyes with papilledema due to raised intracranial pressure to findings in eyes with optic disc swelling due to optic neuritis and nonarteritic anterior ischemic optic neuropathy (NAION), conditions without intracranial hypertension. We measured average thickness of the RNFL and the angle of the RPE/BM at the temporal and nasal borders of the neural canal opening. The angle was measured as positive with inward (toward the vitreous) angulation and as negative with outward angulation.

**Results:** Of 30 eyes with papilledema, 20 eyes (67%) had positive RPE/BM rim angles. One of 8 optic neuritis (12%) eyes and 1 (8%) of the 12 NAION eyes had positive angulation. In 5 papilledema eyes, the RNFL thickening increased, 3 of which developed positive RPE/BM angles. On follow-up, 22 papilledema eyes had reduction of RNFL swelling and 17 of these eyes had less positive RPE/BM angulation.

**Conclusions:** In papilledema, the RPE/BM is commonly deflected inward, in contrast to eyes with NAION or optic neuritis. The RPE/BM angulation is presumed to be due to elevated pressure in the subarachnoid space, does not correlate with the amount of RNFL swelling, and resolves as papilledema subsides.

The authors looked at the line raster scans of swollen optic nerves to determine if the RPE/BM deflected differently between patients with and without papilledema. The angle is formed between the unaltered plane of the RPE/BM and the plane of the peripapillary RPE/BM. The authors also...
Literature Commentary


Objective: Heightened awareness of Creutzfeldt-Jakob disease (CJD) among physicians and the lay public has led to its frequent consideration in the differential diagnosis of patients with rapidly progressive dementia (RPD). Our goal was to determine which treatable disorders are most commonly mistaken for CJD.

Methods: We performed a retrospective clinical and neuropathological review of prion-negative brain autopsy cases referred to the US National Prion Disease Pathology Surveillance Center at the Case Western Reserve University from January 2006 through December 2009.

Results: Of 1,106 brain autopsies, 352 (32%) were negative for prion disease, 304 of which had adequate tissue for histopathological analysis. Alzheimer disease (n = 154) and vascular dementia (n = 36) were the 2 most frequent diagnoses. Seventy-one patients had potentially treatable diseases. Clinical findings included dementia (42 cases), pyramidal (n = 20), cerebellar (n = 14), or extrapyramidal (n = 12) signs, myoclonus (n = 12), visual disturbance (n = 9), and akinetic mutism (n = 5); a typical electroencephalogram occurred only once. Neuropathological diagnoses included immune-mediated disorders (n = 26), neoplasia (n = 25, most often lymphoma), infections (n = 14), and metabolic disorders (n = 6).

Interpretation: In patients with RPD, treatable disorders should be considered and excluded before diagnosing CJD. Misdiagnosed patients often did not fulfill World Health Organization criteria. RPD with positive 14-3-3 cerebrospinal fluid protein should not be regarded as sufficient for the diagnosis of CJD. Adherence to revised criteria for CJD, which include distinctive MRI features of prion disease, is likely to improve diagnostic accuracy.

This study, which comes from the National Prion Disease Pathology Surveillance Center (Case Western Reserve University, Cleveland, OH), is important for neuroophthalmologists who are often the first to diagnose CJD, particularly with the Heidenhain variant. As one might expect, 32% of biopsies in this study were negative for CJD, most commonly in patients with Alzheimer disease or vascular dementia. However, what is surprising is that 23% of patients (71 of 304) had potentially treatable disease. Nine of these patients (13%) had visual symptoms.

A wide spectrum of potentially treatable diseases was found. These included primary angiitis of the CNS (7), acute disseminated encephalomyelitis (6), limbic encephalitis (6), neurosarcoïdosis (4), paraneoplastic cerebellar degeneration (2), Wegener granulomatosis (1), neoplasms (25), fungal infection (5), viral meningoencephalitis (5), parasitic infection (4), and toxic/metabolic encephalopathies (6). One factor that led to a mistaken diagnosis was reliance on a positive 14-3-3 cerebrospinal fluid protein, which the authors point out is sensitive but not specific for CJD and is often positive in other CNS infections. They also point out that recently described MRI findings characteristic for CJD are helpful in making the correct diagnosis.

This study is limited by its retrospective nature and because the data are taken from a national database. Standardized and accurate clinical information on all patients is lacking. Nonetheless, this study heightens our awareness that patients with presentations consistent with CJD may harbor other conditions, which might be treatable and even curable!

—Mark L. Moster, MD

I can see how misdiagnosis of CJD can occur. I think clinicians have an almost knee-jerk reaction to diagnose a patient with a rapidly progressive dementia and a positive 14-3-3 with CJD (similar to the obese young female with papilledema has idiopathic intracranial hypertension). Since CJD is rare, most clinicians do not know the WHO...
diagnostic criteria well, nor realize the low specificity of the 14-3-3 protein.

I looked up the MRI findings suggestive of CJD. They include high signal abnormalities on diffusion-weighted imaging or FLAIR in both the caudate nucleus and putamen OR at least 2 cortical lesions in the temporal, parietal, or occipital lobes (1).

—Michael S. Lee, MD

REFERENCE


Background: Retinal cotton-wool spots (CWSs) are an important manifestation of retinovascular disease in hypertension (HTN) and diabetes mellitus (DM). Conventional automated perimetry data have suggested relative scotomas in resolved CWSs; however, this has not been well delineated using microperimetry. This study evaluates the retinal sensitivity in documented resolved CWSs using microperimetry.

Methods: Retinal CWSSs that resolved after 10–119 months (median, 51 months) and normal control areas were photographed to document baseline lesions. Eye-tracking image-stabilized microperimetry with simultaneous scanning laser ophthalmoscopy was performed over resolved CWSs, adjacent uninvolved areas near the lesion, and in location-matched normal patients (age matched).

Results: A total of 16 eyes in patients with DM or HTN (34 resolved CWSs and 16 normal control eyes (34 areas) were imaged. The mean (SD) sensitivity of resolved CWSs in the eyes of patients with HTN and DM was 11.67 (3.88) dB and 7.21 (5.48) dB, respectively. For adjacent control areas in the eyes of patients with HTN and DM, the mean (SD) sensitivity was 14.00 (2.89) dB and 11.80 (3.45) dB, respectively. Retinal sensitivity was significantly lower in areas of resolved CWSs than in the surrounding controls for patients with HTN (P = 0.01) and those with DM (P < 0.001). Scotomas in patients with DM were denser than those in patients with HTN (P < 0.05).

Conclusions: Cotton-wool spots in patients with DM and HTN leave permanent relative scotomas detected by microperimetry. Scotomas are denser in eyes of patients with DM than in those with HTN. In addition, among patients with DM, adjacent retinas not involved with CWSs have lower retinal sensitivity than in age-matched controls.

The authors used microperimetry to test the sensitivity of the retina in locations where cotton-wool spots had resolved. The ability to eye track and overlay prior fundus photographs ensures accurate localization. As neuro-ophthalmologists, we often receive referrals for unexplained visual field defects. One explanation may be derived from this article—a patient with hypertension or diabetes and a small unexplained relative scotoma could have had a cotton-wool spot that developed and resolved. I also believe that patients with known cotton-wool spots should be counseled about the possibility of permanent relative scotomas.

—Michael S. Lee, MD

This study provides a good foundation for studying the effect of CWS on subsequent visual function. It will be important to evaluate more patients (only 6 patients each with DM and HTN were evaluated) to see if there is truly worse visual field loss in diabetic individuals than those with hypertension. It will also be important to correlate these findings with visual symptoms and with focal retinal thinning, neither of which were done in this study.

—Mark L. Moster, MD


This letter to the editor describes a case of CLIPPERS (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids) syndrome. Although only a case report, I used it as an opportunity to review CLIPPERS, a recently described entity of importance to neuro-ophthalmologists.

In late 2010, Pittock et al (1) described 8 patients with a similar clinical, radiographic, and pathologic picture.

FIG. 1. Curvilinear enhancement “pepperering” the pons on T1 contrast MRI in a patient with CLIPPERS. From Pittock SJ et al (1), with permission from Oxford University Press.

Median age was 45.5 years with a range of 16–86 years. There were 3 men and 5 women. All patients had subacute onset of diplopia and ataxia, and 7 had dysarthria. Five had tingling or altered sensation of the face and scalp. The diplopia was horizontal, but the examination findings were not described.

The characteristic MRI finding was a curvilinear punctate pattern of patchy gadolinium enhancement “peppering” the pons (Fig. 1). These changes may spread to the adjacent brainstem, cerebellum, and spinal cord.

All patients had CSF examinations with mild protein elevation in 4 and a mild pleocytosis in 1. Oligoclonal bands were noted in 3 of 6 patients. Cytology and cultures were negative in all 8 patients.

Four of the 8 patients had brain biopsies, and pathology revealed prominent perivascular infiltration of lymphocytes. Other diseases, including MS, CNS lymphoma, CNS vasculitis, and sarcoidosis, were excluded.

Treatment included intravenous corticosteroids with good initial response but recurrence upon taper, requiring prolonged steroids or immunosuppression. Beneficial medications included mitoxantrone, methotrexate, and azathioprine.

This case adds some new imaging information, although it is not biopsy proven. First, perfusion-weighted imaging showed an increase in perfusion in involved areas to 200%–300% normal, which persisted 3 months later, despite clinical improvement on steroids. Second, severe pontine atrophy was seen at the 20-month MRI.

CLIPPERS is a diagnosis neuro-ophthalmologists need to be aware of. Whether this is a single entity or a clinical phenotype representing numerous underlying etiologies is yet to be determined.

—Mark L. Moster, MD

I had not heard of this entity before; thanks for bringing it up, Mark. Although extremely interesting, CLIPPERS definitely needs a label of “diagnosis of exclusion” even with characteristic MRI findings. Many other entities including CNS lymphoma or infection could present with similar MRI abnormalities and initially respond to corticosteroids. After a nondiagnostic workup, I like the idea that we have a “diagnosis” to give to patients. Yet we are still dealing with limited information on treatment options and prognosis.

—Michael S. Lee, MD

REFERENCE

**Abstract:** Tonic pupils react poorly to light but constrict during viewing of a near stimulus. Adie’s name is typically used in association with tonic pupils, but a review of Adie’s articles reveals that he described the syndrome of tonic pupils and absent reflexes and not the pupillary abnormality per se. Therefore, it would be more appropriate to refer to a tonic pupil as simply a “tonic pupil” and leave Adie’s name for the syndrome.

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Today, a tonic pupil—a nonsyphilitic pupil that poorly reacts to light but contracts slowly to a near stimulus and slowly redilates—is often labeled an “Adie pupil,” and the symptom complex of a tonic pupil with absent deep tendon reflexes are labeled as “Adie syndrome.” These eponyms give credit to William John Adie (Fig. 1), an Australian-born neurologist who practiced in London in the early 20th century (1). However, a close reading of Adie’s publications on the topic shows that Adie made little attempt to contribute to the literature on the tonic pupil, that its features were largely known prior to his publications, and that it is more appropriate to refer to the abnormal pupil as a “tonic” rather than as an “Adie” pupil.

In May 1931, Adie (2) published his first article on the tonic pupil (Fig. 2), which was a report of 5 patients he examined and a sixth case previously reported by Gehrcke (3,4). He made no claim to add to the existing literature on the tonic pupil, writing the “myotonic reaction is well known to ophthalmologists, and it has been firmly established that syphilis plays no part in its production” (2). Rather, Adie wrote at the beginning of this article, “I wish to draw attention to a benign symptomless disorder characterized by pupils which react on accommodation but not to light, and by absent tendon reflexes” (2). He felt this combination of symptoms was a new contribution to the literature as he knew of only 2 published cases, Gehrcke’s 1 case and 1 case by Moore (5), in which a patient was noted to have an abnormal pupil and absent tendon reflexes.

The following year, Adie expanded on his case report and published 2 articles discussing the disorder that we now refer to as “Adie syndrome” (6,7). In a 1932 article published in Brain (6), he wrote that there was a “complete form” of his syndrome “characterized by the presence of the tonic pupillary reaction in its most characteristic form and absence of 1 or more of the tendon reflexes.” He also delineated 4 “incomplete forms,” which include “(a) tonic pupil alone; (b) atypical phases of the tonic pupil alone (‘iridoplegia’; ‘internal ophthalmoplegia’); (c) atypical phases of the tonic pupil with absent reflexes; and (d) absent reflexes alone” (7). These “incomplete forms” expanded the definition of Adie syndrome so that many patients, even with differing symptoms, in his opinion could be diagnosed as having an atypical form of the syndrome (8).

Adie argued that many of the previously reported cases with tonic pupils might actually have had an incomplete form of his syndrome. He wrote, “I feel sure that if the patients described by Foster Moore and by Morgan and Symonds were re-examined it would be found in the first group, where the tonic pupillary reactions were detected, that many of the patients also have loss of reflexes” (6).

Thirty-three years later, Lowenstein and Lowenfeld (8) published a comprehensive review on the tonic pupil chronicling its initial description in the scientific literature and the subsequent discoveries that contributed to our understanding of the phenomenon. They credit the first description of the tonic pupil to Ware in 1812 (9), as he described a patient who likely had the condition—a woman with a single dilated pupil that did not respond to light but did contract to a near stimulus—even though Ware did not focus on the tonic pupil’s features. The first major set of...
articles published on the subject were at the turn of the 20th century when Piltz (10,11), Strasburger (12), and Saenger (13) began describing the characteristics of this pupillary disorder. These authors described a nonluetic pupil with abnormally long-lasting pupillary constriction to the light reflex, or absent light reflex, paired with slow extensive contraction to a near stimulus and sluggish redilation upon returning to a far stimulus. In the early 20th century, Markus (14,15) gave the first description in the English literature of 2 patients whose pupils did not react to light but became “quite small” while viewing a near stimulus and subsequent redilation was prolonged. Over the next 15 years, other cases with tonic pupils were detailed (8).

Lowenstein and Lowenfeld (8) critically argued that many of the characteristics of the tonic pupil were known prior to Adie’s publications, including its increased prevalence in women, unilateral presentation, etiology other than syphilis, and characterization by an abnormally reacting iris sphincter. They concluded in their review that Adie “had no priority for any one of the features of the pupillotonic syndrome which bears his name” rather “it was Adie’s main contribution to have focused interest upon this syndrome.” Furthermore, we share Lowenstein and Lowenfeld’s skepticism that Adie’s claim that instances of isolated tonic pupils or isolated absent deep tendon reflexes are incomplete “atypical forms” of his syndrome.

We are not the first to suggest that isolated tonic pupils should be distinguished from those associated with defective deep tendon reflexes. In his personal series, Thompson (16) did separate tonic pupils due to known ocular or orbital disease, such as trauma (“local tonic pupils”), those due to generalized neuropathic conditions, such as diabetes (“neuropathic tonic pupil”), and those due to “obscure origin,” which he labeled as having “Adie’s syndrome.” However, of 122 patients he included in this last group, 114 had reduced or absent deep tendon reflexes, while 8 had normal reflexes! He called these 8 patients as having “Adie’s with normal reflexes.” While consistent with Adie’s original classification, we would suggest that these patients simply had “tonic pupils” without having a syndrome.

Parenthetically, it could also be argued that Adie was not the only author to suggest an association between a tonic pupil and absent reflexes. For instance, one of Markus’ patients reported in 1905 (14) also exhibited absent knee jerks, which Markus noted but did not extensively comment upon. Also in 1931, Holmes (17) reported 19 patients having tonic pupils associated with loss of deep tendon reflexes, prompting many to call this the Holmes–Adie syndrome.

In no way are we advocating that eponyms be abandoned. Instead, we are recommending that we attribute a named syndrome or disease correctly to what the person actually described (18,19). Eponyms add color, humanism, and a historical basis to our medical diagnoses, and the shortened terminology facilitates communication among physicians and patients (20). Although the use of eponyms has been discouraged because in part they may be too nebulous or honor infamous individuals (21), designations such as Alzheimer disease, Parkinson disease, Babinski sign, and Susac syndrome will always be part of our neurologic and ophthalmologic lexicon. Certainly, these eponymic designations are preferred to dementia due to neuritic plaques and tangles; bradykinesia, tremor, and rigidity due to dopaminergic neuron depletion; large toe extension following plantar stimulation; and idiopathic retinocochleocerebral microangiopathy. Eponyms do not necessarily have to be ascribed to the person who provided the first description but rather to honor the person(s) who clarified, synthesized, or popularized the disorder, syndrome, or sign.

Thus, upon closer inspection of the historical record, Adie was neither the first to describe the tonic pupil, nor did he do anything more than make it part of his syndrome. He understood that the characteristics of the tonic pupil were well established when he published on the subject. In summary, it would be more appropriate to refer to a tonic

**FIG. 1.** William John Adie, MD, FRCP (22).

**FIG. 2.** Seminal publication on the association of tonic pupils with diminished deep tendon reflexes (2).
pupil as simply a “tonic pupil” and leave Adie’s name for the syndrome he carefully described and popularized.

ACKNOWLEDGMENT

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REFERENCES

Arthur H. Wolintz, MD (1937–2011)

On August 22, 2011, the neuro-ophthalmology community lost a giant. Arthur H. Wolintz, MD, passed away at the age of 74 from complications of multiple myeloma.

My father was born in Brooklyn, New York. He attended public school and majored in history at New York University, completing his studies in 3 years. He graduated summa cum laude from Downstate Medical Center and was selected to the Alpha Omega Alpha (AOA) Honor Medical Society.

He became a house officer at Maimonides Medical Center with the goal of becoming a cardiologist. But after studying at the National Institute of Neurological Diseases and Blindness, he turned to neurology, completing a residency (and chief residency) at Mount Sinai Hospital in New York. There, he came under the spell of Morris Bender, MD, the brilliant phenomenologist, who induced him to take a fellowship in neuropathology at Columbia University.

He returned to Brooklyn to join the faculty at SUNY Downstate and Maimonides Medical Center. Soon he realized that his passion lay in how the eye relates to the brain. He decided to do a residency in ophthalmology at Downstate Medical Center, later becoming one of the first neuro-ophthalmologists to be board certified in both neurology and ophthalmology.

He went on to author a textbook titled Essentials of Clinical Neuro-Ophthalmology, over 55 peer-reviewed articles, and several book chapters. He served on the staff of nearly every hospital in Brooklyn, creating and chairing the Department of Ophthalmology at Downstate Medical Center and Kingsbrook Jewish Medical Center for a quarter of a century and establishing a much sought-after clinical rotation and fellowship in neuro-ophthalmology.

The recipient of numerous teaching awards, he received the honor of Distinguished Teaching Professor in the University System of the State University of New York in 1997. In 1992, the SUNY medical students selected him as counselor of their AOA chapter.

He taught, influenced, inspired, and mentored hundreds of students, residents, fellows, and colleagues. To his residents and fellows, he was not just a mentor but also a second “father” who helped them obtain positions and continued to guide them for years afterward.

He would request reprints of his favorite articles from medical journals and store them in enormous files. If you mentioned a topic, he could find the pertinent original papers and hand them to you. The keeper of those files was his wife Carol, who managed his neuro-ophthalmology office for more than 40 years. To my father, “don’t leave the house without it” meant “don’t leave without Carol.”

My father knew all his patients by name, and he could talk to them about family matters and their personal interests. He instructed me to always make sure that the waiting room was posted the following notice: “Waiting is a nuisance, but I promise that you will receive my careful attention.”

When my father was not practicing neuro-ophthalmology, he was studying Judaism or worshipping in that faith. He celebrated his Bar Mitzvah at the Flatbush Jewish Center and essentially never left. Able to chant any portion from the Torah or Haftorah without any preparation, he ran the auxiliary services on Rosh Hashanah and Yom Kippur every year of his adult life.

He shaped my approach to medicine, to neuro-ophthalmology, and to life. Before I could even read, he took me on weekend rounds with Dr. Morris Bender, Chair of the Department of Neurology at Mount Sinai Hospital in New York. When he started his ophthalmology residency, he taught me how to use a direct ophthalmoscope. When I began my neurology rotation as a medical student, his eyes would shine with each case we discussed.

Dad did not travel very much, but one of his last trips was to the North American Neuro-Ophthalmology Meeting in Tucson, Arizona, in 2010. In the past, when we attended such meetings together, I was always in awe of the people he knew and the respect they had for him. At the meeting in Tucson, he told me how proud he was of being known as “the father of Dr. Robyn J. Wolintz.”

I am proud to be able to say that Arthur H. Wolintz, MD, was not just my mentor and my friend but most importantly my father.

Robyn J. Wolintz, MD
Importance of Clinical Judgment in the Diagnosis of Temporal (Giant Cell) Arteritis

I attended the Walsh session at the 35th Annual NANOS meeting in Lake Tahoe in 2011, where the very interesting case report “Occult Temporal Arteritis in a 54-Year-Old Man” by Levin et al (1) was first presented, and I was happy to see it is published.

In 2008, at the Annual Meeting of the American Academy of Ophthalmology, we presented our review of 3,001 temporal artery biopsies performed in the Kaiser Foundation Health Plan from 1997 to 2006. We found 17 of 459 positive biopsies in the 50–59 years old range, and of these, only 3 were in men. What is even more remarkable about the patient reported by Levin et al is that his erythrocyte sedimentation rate, C-reactive protein, and platelet count were normal. At the 2010 Annual Meeting of the American Academy of Ophthalmology, we reported on the prevalence of positive temporal artery biopsies in the setting of normal laboratory values. Of the 459 patients with positive temporal artery biopsies, 20% had a normal erythrocyte sedimentation rate, 5% had a normal C-reactive protein, and 55% had normal platelets. We found that only 2 of the 459 patients had all the 3 laboratory values within normal limits (although not all patients had all 3 tests performed).

Giant cell arteritis is primarily a disease of elderly white women with abnormal laboratory test results supporting the diagnosis. Levin et al remind us that a high index of suspicion is essential in making the diagnosis of giant cell arteritis.

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The author reports no conflicts of interest.

REFERENCE

Erratum

In the Letter to the Editor (1) titled “Atypical central serous chorioretinopathy with peripapillary subretinal fluid suggesting an optic neuropathy,” an author was inadvertently omitted. The second author is Vivek R. Patel, MD, University of Ottawa Eye Institute, Ottawa, Canada. Dr. Patel reports no disclosures. The authors regret the error.

REFERENCE
Demyelinating Disorders of the Central Nervous System in Childhood
Dorothee Chabas and Emmanuelle L. Waubant. Cambridge University Press; 2011. 278 pages, Hard cover, 23 chapters. $110
ISBN: 0521763495

Referenced
Intended audience: Neurologists, neurosurgeons, pediatric neurologists, pediatricians, and neuro-ophthalmologists.

This multiauthored text provides comprehensive coverage of demyelinating diseases of childhood, highlighting the differences in the management of these disorders between children and adults. Chapters are dedicated to the diagnosis, course, treatment, and biology of pediatric multiple sclerosis and include other childhood demyelinating diseases, such as acute disseminated encephalomyelitis, optic neuritis, acute transverse myelitis, and neuromyelitis optica.

Printed on high-quality paper, there are 35 black and white illustrations, 7 color illustrations (of pathologic specimens located at the end of the book), and 46 tables. This unique text is a valuable resource for the physician who cares for patients with pediatric demyelinating disease.

Multiple Sclerosis: Recovery of Function and Neurorehabilitation
ISBN: 0521888328

Referenced
Intended audience: Neurologists, rehabilitation physicians, neurophysiologists, and neuro-ophthalmologists.

Written by world experts in the field of multiple sclerosis, this text focuses on the mechanisms of neurologic recovery and application of neuroplasticity to therapeutic interventions. This book achieves an excellent balance between basic science, pathophysiology, and clinical rehabilitation.

The book is organized in 4 main sections: 1) basic mechanisms of MS, 2) assessment of mechanisms and disease status, 3) and 4) various aspects of neurorehabilitation. Chapters include evoked potentials, physiopathology, synaptic changes and sodium channel expression and function in MS, basic mechanisms of functional recovery, the adult human oligodendrocyte precursor cell, tissue regeneration and repair, and MRI to assess gray matter damage in multiple sclerosis.

Mostly illustrated in black and white with multiple tables, graphs, and a few color photographs, this text presents a novel approach and valuable resource for physicians who treat patients with multiple sclerosis.

Neurological Complications of Systemic Cancer and Antineoplastic Therapy
Herbert B. Newton and Mark G. Malkin. Informa Healthcare; 2010. 590 pages, Hard cover, 29 chapters. $324
ISBN-10: 0849391911

Referenced
Intended audience: Neurologists, oncologists, neurosurgeons, ophthalmologists, and neuro-ophthalmologists.

This multiauthored book provides an in-depth review of the neurololgical complications of various cancers including lung, breast, gynecological, genitourinary, and melanoma. The text covers common problems like brain metastases, spinal cord compression, cerebrovascular events, and leptomeningedisease, as well as more unusual topics such as paraneoplastic disorders, neoplastic plexopathy, metastatic spread to cranial and peripheral nerves, and neurological complications of immunotherapy, bone marrow transplantation, radiation, and chemotherapy.

Of particular interest to the neuro-ophthalmologist are the chapters on cranial nerve involvement by metastatic cancer, paraneoplastic disorders, and head and neck cancer.

The book is illustrated in color and black and white, with high-quality MRI and pathology photographs (mostly in color), tables, and illustrations. It serves as an authoritative reference in the field of neuro-oncology.
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