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Instructions for Authors appear in the March issue or online at www.jneuro-ophthalmology.com.
A CR(l)MP in the Optic Nerve: Recognition and Implications of Paraneoplastic Optic Neuropathy

Preston C. Calvert, MD

Paraneoplastic optic neuropathy (PON) is a rare cause of visual loss in patients with cancer. The clinical picture of PON usually begins with subacute or acute loss of vision in one or both eyes (1). Visual acuity can be reduced to any degree, sometimes to profound levels. There are other signs of optic nerve dysfunction such as color perception deficits and optic nerve-related visual field loss. Optic disc swelling may occur. A posterior vitreous cellular reaction is frequently present.

PON is almost always associated with other evidence of neurologic dysfunction such as cerebellar ataxia, polyneuropathy, dysgeusia, anosmia, involuntary movement disorders, autonomic dysfunction, and myelopathy. PON and associated neurologic manifestations may occur in a patient with known cancer or may be the presenting sign of underlying systemic neoplasia. The underlying tumor is most often small cell lung carcinoma, although the condition has been associated with other tumors, including non-small cell lung carcinoma, renal carcinoma, and thyroid carcinoma (1).

PON was recognized as a distinct disease entity by its clinical features and by the lack of electrophysiological evidence characteristic of paraneoplastic retinal degeneration. Electroretinography does not show abnormalities consistently in patients with PON, although amplitude reduction in photopic responses can be seen (2). By contrast, both photopic and scotopic responses are usually markedly attenuated in typical cancer-associated retinopathy (3). Melanoma-associated retinopathy has unique electroretinography features that are not seen in patients with PON, particularly attenuation of B waves with relative preservation of A waves in both the scotopic and photopic responses, reflecting functional impairment of rod bipolar pathways in the retina similar to those of congenital stationary night blindness (4). In patients with PON, visual evoked potentials often show conduction delay (1).

Cerebrospinal fluid examination in PON usually shows lymphocyte-predominant reactive pleocytosis with white cell counts in the range of 20 to 50 (range of 0-122 has been reported), elevated total protein (usually 50–120 mg%), and oligoclonal immunoglobulin bands on electrophoresis (1). Cerebrospinal fluid cytology shows no evidence of direct meningeal infiltration. Examination of the pathologic optic nerves in a few cases (5,6) has shown findings of perivascular inflammation and associated demyelination. Similar findings have been seen in many other central nervous system areas, including medial temporal lobe, cerebellum (with Purkinje cell loss), brainstem, and spinal cord (1,5,6). Peripheral nerve structures may also be involved (1).

Examination of the serum has shown IgG antibodies directed against an antigen expressed in neural tissues and associated tumors. Although a number of apparently different antigen specificities have been reported, they have all been shown to be...
indistinguishable from the 62 kDa collapsin response-{
mediator protein-5 (CRMP-5) (7-9). The CRMP-5 antigen
is expressed in many central and peripheral tissues by neu-
rons and supporting cells. It is also regularly expressed in
small cell lung carcinoma cytoplasm, providing an explana-
tion for the crossreactivity of the antitumoral immune
response with host neural tissues. The widespread expres-
sion of CRMP-5 in central and peripheral nervous system
cells presumably accounts for the wide range of neurologic
impairments in patients with PON. There are cases of PON
that do not show CRMP-5 reactivity, presumably related
to other antigens shared by optic nerve and tumor cells.
Continued laboratory serum screening may yield additional
target antigens.

In this issue of the Journal of Neuro-Ophthalmology,
Sheorajpanday et al (10) report a case of PON as an isolated
presenting manifestation of CRMP-5-mediated autoimmu-
ity. Discovery of the antibody led to the diagnosis of small
cell lung carcinoma. Isolated PON as the presenting feature
has been reported only rarely (1,11). Neuropathologic ex-
amination of the optic nerves showed features typical of
those reported previously in PON; regretfully, pathologic
examination of the rest of the brain in their case did not
occur.

The visual prognosis of patients with PON is reported
to be quite variable. Some patients progress to severe visual
loss despite treatment of the underlying tumor and efforts at
immunosuppression (1). This was unfortunately true in the
case of Sheorajpanday et al (10). Other patients have an
apparent beneficial effect on their visual function after
effective treatment of the underlying tumor (1,12). Such
improvement can occasionally be dramatic (12). The poten-
tial responsiveness of PON to tumor treatment emphasizes
the importance of early recognition of this entity so that the
underlying tumor can be quickly identified and treated.

Although there usually will be other neurologic mani-
festations such as progressive ataxia, myelopathy, or demen-
tia associated with optic neuropathy to suggest a para-
neoplastic syndrome, the case of Sheorajpanday et al (10)
highlights the need to think of PON even when subacute or
acute optic neuropathy is isolated. In their case, small cell
lung carcinoma was apparent on routine chest radiography,
but if such a study is negative in a patient with suspected
PON, a chest CT should be considered as well as fluoro-
deoxyglucose positron emission tomography because small
cell lung cancers can be difficult to detect (1). If no evidence
of a lung tumor is found, one should consider other sites
such as the thyroid gland, nasopharynx, kidney, and possibly
thyroid gland. A serum assay for anti-CRMP-5 anti-
body should be obtained immediately when the diagnosis is
entertained. The CRMP-5 antibody assay, developed at the
Mayo Clinic, is available for clinical testing through the
Mayo Clinic Laboratories by submitting a standard serum
specimen (9,13). Situations that should suggest this diag-
nosis when isolated optic nerve disease is present include
acute or subacute onset and progressive course of unilateral
or bilateral optic neuropathy that remains unexplained after
detailed history, examination, and initial ancillary evalua-
tion. The presence of posterior vitreous cells with optic disc
swelling in the absence of other apparent causes of inflam-
matory optic neuropathy such as sarcoidosis, infectious
meningitis, or known systemic infection or autoimmune
disorder should also raise the question of PON.

Treatment of PON with corticosteroids has produced
variable results (1,12,14). As noted previously, many
patients experience no improvement or progressive decline
in vision despite all treatment efforts. However, visual
improvement has been reported after use of different
corticosteroid regimens, including oral prednisone in doses
of 60 mg per day (14) and 1,000 mg intravenous methyl-
prednisolone per day for 5 days (12). One patient with PON
was reported to have shown dramatic visual improvement
after being treated with intravenous immunoglobulin
(IVIg), although another patient in the same report showed
no change in visual acuity with the same regimen (2). The
limited reported anecdotal experience does not permit firm
recommendations about treatment of PON beyond the need
to identify the underlying tumor rapidly and, if possible,
treat it. Given the frequency of devastating permanent
visual loss in PON, one should consider a trial of corti-
coesteroid treatment possibly initiated by intravenous high-
dose methylprednisolone and followed by a course of IVIg.

The degree of permanent axonal loss that has occurred
due to the time of diagnosis and initiation of treatment probably
influences the outcome.

REFERENCES
optic neuritis with retinitis defined by CRMP-5 IgG. *Annu Neurol*
2. Gay J, Apsilauri N. Treatment of paraneoplastic visual loss with
intravenous immunoglobulin: report of 3 cases. *Arch Ophthalmol*
in paraneoplastic retinopathy. *Graefes Arch Clin Exp Ophthalmol*
in paraneoplastic night blindness with cutaneous malignant
and 'optic neuritis': paraneoplastic effects of bronchial carcinoma.
6. Boghen D, Sebag M, Michael J. Paraneoplastic optic neuritis and
137-41.
syndrome and optic neuritis with anti-CV2 antibodies: clinical
response to excision of the primary tumor. *Arch Neurol* 1999;56:
405-8.


Small Cell Lung Carcinoma Presenting as Collapsin Response-Mediating Protein (CRMP) -5 Paraneoplastic Optic Neuropathy

Rishi Sheorajpanday, MD, Hans Slabbynck, MD, Wivine Van De Sompel, MD, Danny Galdermans, MD, Ingrid Neetens, MD, and Peter Paul De Deyn, MD, PhD

Abstract: A 77-year-old woman presenting with progressive visual loss in both eyes was found to have small cell lung cancer. Assay for collapsin response-mediating protein (CRMP) -5 was positive suggesting a paraneoplastic optic neuropathy (PON). During treatment of the small cell lung cancer, the patient died of pneumonia and autopsy disclosed neuropathologic abnormalities consistent with PON. This is only the second case of CRMP-5-confirmed PON to report neuropathologic findings.

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CASE REPORT

A 77-year-old woman was admitted to our neurologic ward because of progressive painless visual loss of the right eye for 2 months. Visual acuity in the left eye had been documented at finger counting for several years. Our examination showed finger counting acuity in both eyes. Direct and consensual pupil reactions were normal in the right eye. In the left eye, however, the pupil light reaction was very weak. Biomicroscopic examination was normal apart from bilateral cataract. Applanation tonometry was 16 and 19 mm Hg. Ophthalmoscopy of the right eye revealed a swollen optic disc with ill-defined margins and multiple peripapillary hemorrhages with a normal-appearing macula (Fig. 1). Ophthalmoscopy of the left eye disclosed a pale, indistinct optic disc.

Within one week, visual acuity deteriorated to light perception in the right eye and to hand movements in the left eye. Ophthalmoscopy showed small vitreous cells. There were cotton wool spots at the inferior margin of the right optic disc. There were no cells in the anterior chamber. Ophthalmoscopic examination of the left eye was unchanged. Neurologic examination was otherwise normal.

A chest x-ray revealed a 5.5 × 5.5-cm mass in the right upper lobe. CT disclosed the mass in the absence of mediastinal invasion or lymphadenopathy (Fig. 2). Complete blood count, electrolytes, and acute-phase reactants were normal. Whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) suggested tumor activity in the apex of the right lung, the right parotid–submandibular junction, and in the left nasopharynx. CT suggested a benign salivary gland tumor. Nasopharyngeal mucosal biopsy was negative for neoplasm. Needle biopsy of the lung lesion disclosed undifferentiated small cell carcinoma (SCLC).

Brain MRI was normal except that it showed hyperintense signal on T2 imaging and mild enhancement of the right optic nerve (Fig. 3).
CRMP-5 Paraneoplastic Optic Neuropathy


FIG. 1. Bedside fundus photography shows marked optic disc edema in the right eye with papillary hemorrhages and a pale, indistinct optic disc in the left eye.

FIG. 2. Chest CT shows a large mass (arrow) in the right upper lobe that proved to be small cell carcinoma.

Lumbar puncture showed a normal opening pressure and acellular fluid with a normal glucose but an elevated protein at 84 mg/dL. Cytology was negative. There was an oligoclonal banding pattern in the gamma globulin region; by isoelectrofocusing, 7 cerebrospinal fluid (CSF)-specific oligoclonal fractions between pH 7 and 8.6 were detected. Duplex imaging showed normal flow in both ophthalmic arteries. Anti-neuronal antibody assay was positive for anti-CRMP-5 but not for anti-Hu, anti-Yo, anti-Ri, anti-amphysine, anti-Ma, and anti-Tr, and was negative for anti-calcium channel antibodies.

Cisplatin–etoposide chemotherapy and radiotherapy for the lung tumor resulted in decreased tumor volume on subsequent CT. Visual acuity, however, deteriorated further to light perception bilaterally. Ophthalmoscopic examination after 2 months revealed bilateral disc pallor without swelling and with small-caliber retinal vessels. Neurologic examination 2 and 4 months later still disclosed no other abnormalities. Four months after presentation, the patient died of overwhelming pneumonia.

General autopsy disclosed an irregularly margined tumor with a maximum diameter of 1.5 cm in the right upper lung lobe. Microscopic examination revealed extensive regions of necrosis with foamy macrophages, lymphocytes, monocytes, and plasma cells but no viable tumor cells. There were no macroscopically detectable metastases. Neuropathologic examination, limited to the optic nerves, disclosed thickening of the right optic nerve with reactive changes consisting of spongiosis, perivascular edema, and perivascular lymphocytic infiltration mostly positive for CD3 and CD20 without any signs of metastasis (Fig. 4). These findings were interpreted as consistent with chronic PON.

FIG. 3. A. Postcontrast T1 coronal MRI demonstrates a relatively enlarged and enhancing right optic nerve (arrow) as compared with the left optic nerve (arrowhead). B. T2 coronal MRI shows that the right optic nerve has relatively high signal compared with the left optic nerve.

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FIG. 4. Autopsy findings. A. Cross-section of the swollen right optic nerve shows spongiosis and perivascular lymphocytic infiltration. B. Cross-section of the left optic nerve shows minimal changes (hematoxylin and eosin, scale bar = 1,000 µm). C. Microscopic section of the right optic nerve shows prominent spongiosis (S) and perivascular lymphocytic infiltration (arrow). D. Similar but much less evident changes are present in the left optic nerve (hematoxylin and eosin, scale bar = 100 µm). E. Immunohistochemistry for the pan-T-cell marker CD3 of the right optic nerve is clearly positive (scale bar = 200 µm). F. Immunohistochemistry for CD20 in the same right optic nerve area is also positive (scale bar = 200 µm).
DISCUSSION

In the estimated 25 reported cases of PON, most patients have also displayed ophthalmoplegia (2–5), retinitis, multifocal neurologic deficits (1), or a cerebellar syndrome (6–9). Our patient with CRMP-5 PON is unusual in presenting with isolated bilateral optic neuropathy after which a diagnosis of SCLC was made. A seemingly similar case of isolated PON in previously diagnosed non-small cell lung carcinoma was recently reported (10). In this case, however, the diagnosis was not confirmed with anti-neuronal antibody.

PON produces unilateral or bilateral progressive visual loss with optic disc edema followed by disc pallor and accompanied by lymphocytosis and protein elevation in the CSF (11). In our patient, ophthalmoscopic findings initially suggested the possibility of intraocular lymphoma for which a diagnostic vitrectomy was planned. However, once the lung mass was detected, we considered PON and elected to draw an anti-neuronal antibody assay. Once anti-CRMP-5 antibody was confirmed, vitrectomy was not necessary. Hoh et al. (12) described a case of PON in nasopharyngeal carcinoma (12), but pathologic examination of the nasopharynx in our patient revealed no neoplasia.

Anti-CRMP-5 antibodies are most commonly associated with SCLC. Also implicated are other types of bronchial carcinoma, nasopharyngeal carcinoma, Hodgkin and non-Hodgkin lymphoma, neuroblastoma, pancreatic glucagonoma, and thymoma (13). The pathophysiological mechanism by which anti-CRMP-5 antibodies cause optic neuropathy remains unclear. Because CRMP-5 is expressed in SCLC (1,13,14), the most plausible pathogenetic mechanism of PON in SCLC is an immune response against the onconeural antigen. There is still no adequate pathogenetic explanation for the wide range of neurologic manifestations with which CRMP-5-seropositive patients present (optic neuropathy, other cranial neuropathies, retinitis, cerebellar degeneration, diverse forms of encephalomyelitis [1,13]). Of the 116 CRMP-5-seropositive patients reported by Yu et al. (14), 8 had optic neuropathy; in only 3 of these cases was optic neuropathy the initial presentation.

Therapy of paraneoplastic syndromes is often directed at the tumor, although a significant number of patients experience irreversible damage. The neurologic manifestations often remit, although not completely, after treatment of the malignancy. In our patient, there was a rather rapid evolution from optic disc swelling to atrophy under chemotherapy. Direct treatment of the paraneoplastic syndrome with intravenous immunoglobulin, not tried in our patient, has produced mixed results (15). It is not useful in severely disabled patients with anti-neuronal antibodies (16). Neuropathologic examination in our patient was typical of previously described cases of PON (1,2,5,6).

Of special interest are the findings described by Cross et al. (1) in the only other CRMP-5-positive PON with neuropathologic examination. Histopathologic examination of the eye and optic nerve from that patient showed chronic optic neuritis with inflammatory infiltrates composed predominantly of T cells, most of which were CD8+. Patchy loss of axons and myelin was associated with the inflammatory infiltrates (1). That patient, with metastatic small cell carcinoma in a hilar lymph node, however, also had dementia, partial complex seizures, limited upgaze, and myelopathy with numerous white matter lesions on brain MRI and a patchy high-intensity T2 signal on spinal cord MRI. Neuropathologically, there was marked involvement of medial temporal structures (particularly amygdala), cerebellum, brainstem, and spinal cord. Mild loss of myelinated axons was noted in peripheral nerves, spinal rootlets, and spinal sensory ganglia at all levels (1). Most interestingly, that patient also harbored anti-N-type calcium channel antibodies (1). It is possible that these anti-N-type calcium channel antibodies contributed to the findings in that patient. Additional analysis for anti-calcium channel antibodies was negative in our patient. Perhaps our case is the first PON with neuropathologic findings attributable to anti-CRMP-5 antibodies alone. Further research is necessary to elucidate the exact nature of anti-CRMP-5-associated PON.

REFERENCES


Unilateral Midbrain Infarction Causing Upward and Downward Gaze Palsy

Murat Alemdar, MD, Senol Kamaci, MD, and Faik Budak, MD

Abstract: We report on a 47-year-old-woman who developed sudden complete loss of vertical saccades, smooth pursuit, and vestibular eye movements bilaterally. MRI revealed a unilateral midbrain infarct involving the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and the interstitial nucleus of Cajal (INC) and spared the posterior commissure (PC). The lesion is presumed to have interrupted the pathways involved in vertical gaze just before they decussate, inducing an anatomically unilateral but functionally bilateral lesion. Previous reports of bidirectional vertical gaze palsy have shown lesions involving the PC or both riMLFs. This case is the first to show that a unilateral lesion of the riMLF and the INC that spares the PC may cause complete bidirectional vertical gaze palsy.

(J Neuro-Ophthalmol 2006;26:173-176)

The posterior commissure (PC), interstitial nucleus of Cajal (INC), and rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), neural structures of the reticular formation of the midbrain, are involved in the mediation of vertical gaze. Vertical gaze deficits after a unilateral midbrain lesion have been identified in prior reports (1,2). This single case reveals for the first time that a unilateral lesion that involves the riMLF and INC but spares the PC can paralyze upward and downward saccades, smooth pursuit, and the vestibulo-ocular reflex.

We report on a 47-year-old woman who developed sudden vertical gaze palsy consisting of bilateral complete loss of upward and downward saccades, smooth pursuit, and vestibular eye movements. Brain MRI studies revealed a unilateral ischemic midbrain infarct sparing the PC but involving the riMLF and INC.

CASE REPORT

A 47-year-old woman developed sudden diplopia worse when looking up or down. She had no associated nausea, vomiting, vertigo, or weakness. Neurologic examination revealed complete upward and downward gaze palsy on voluntary saccadic and pursuit eye movements (Fig. 1). Vertical oculocephalic maneuver did not elicit any upward or downward response. Bilateral caloric stimulation to test for the vestibular response was also impaired. Bell phenomenon, horizontal eye movements, and convergence were preserved. Motor and sensory examinations were completely normal.

Brain MRI on the third day after symptom onset revealed acute infarction of the right upper midbrain in the region containing the riMLF, INC, red nucleus, and substantia nigra pars compacta but sparing the PC (Fig. 2). Magnetic resonance angiography did not show stenosis of the vertebral or basilar arteries. Pericranial and transcranial Doppler studies were unremarkable. Transthoracic echocardiography detected mitral stenosis and an enlarged left atrium. Transesophageal echocardiography did not reveal any thrombus or septal defect. She was treated with antiplatelet medication.

Neuro-ophthalmologic examination 6 months after symptom onset revealed only a slight improvement in downward saccadic and pursuit movements.

DISCUSSION

Our patient had an impairment of all types of upward or downward eye movements: saccadic, pursuit, and vestibular. MRI showed a high-intensity area limited to the medial side of the right midbrain region involving the riMLF and INC but not the PC. The diffusion-weighted images confirmed the area of acute infarction as sparing the PC.

Cases of vertical gaze palsies in association with a unilateral upper midbrain lesion without PC involvement have seldom been reported (3,4). They differ from our case in that vestibulo-ocular eye movements were preserved. Our report confirms that a unilateral midbrain lesion can...
FIG. 1. Position of the patient's eyes in (a) straight ahead gaze, (b) left gaze, (c) right gaze, (d) attempted upgaze, and (e) attempted downgaze.

paralyze not only upward and downward saccades and smooth pursuit, but also the vestibulo-ocular reflex.

Vertical saccades are generated by burst neurons lying in the riMLF, a wing-shaped nucleus lying dorsomedial to red nucleus, rostral to the oculomotor nucleus, and ventral to the periaqueductal gray matter (5) (Fig. 3). Combined upward and downward gaze palsies have been attributed to bilateral infarctions involving both riMLFs resulting from occlusion of a single posterior thalamostriatal paramedian artery (5–7). However, two reports confirmed by neuroimaging–neuropathologic correlation (1,4) have provided evidence that a unilateral lesion in the midbrain can paralyze both upward and downward gaze.

The projections from the riMLF to oculomotor neurons innervating elevator muscles (superior rectus and inferior oblique) appear to be bilateral with collaterals probably crossing within the oculomotor nuclear complex. Projections to motoneurons supplying the depressor muscles (inferior rectus and superior oblique), however, appear to be ipsilateral. Thus, riMLF lesions cause conjugate saccadic palsies that are usually either complete or selectively downward, whereas bilateral riMLF lesions abolish all vertical and torsional saccades. Other types of eye movements are preserved (8,9). Downward gaze is mediated by fibers that travel ventrally to the ipsilateral inferior rectus subnucleus and contralateral superior oblique nucleus. Although a unilateral midbrain lesion would not be expected to affect bilateral vertical eye movements, at least not the upward gaze component (10), such a phenomenon has been reported (1,2,4). There are also reports of lesions producing bidirectional vertical gaze palsy that completely spare the midbrain but involve the thalamus (5). Therefore, although this scheme of vertical eye motility is useful clinically, it is still speculative.

Ranalli et al (1) first reported a patient with paralysis of upward saccades, decreased amplitude and velocity of downward saccades and vertical smooth pursuit, and decreased gain and amplitude of the vestibulo-ocular response. In that case, neuropathologic examination demonstrated that the right riMLF, part of the INC, and the nucleus of the PC were involved but the PC tract was spared. They hypothesized that downgaze fibers might partly decussate in the vertical commissure and traverse the region of the opposite riMLF (1). Recent experimental studies have confirmed this view and shown that bilateral lesions of the INC not only impair gaze-holding ability, but also greatly reduce the range of vertical eye movements (11).

Bogousslavsky et al (4) have described a patient with combined upgaze and downgaze palsy in association with an upper midbrain infarct limited to the right riMLF. They suggested that a unilateral riMLF lesion may have disrupted bilateral upgaze excitatory and inhibitory inputs and unilateral downgaze excitatory inputs. Paralysis of vertical saccades in our case may also be explained by complete loss of burst cells in the right riMLF and interruption of crossing fibers from the left riMLF as they traverse the right midbrain tegmentum.
Vertical pursuit signals are known to traverse the rostral midbrain before innervating ocular motor nuclei. Neuronal firing related to vertical pursuit pathways has been recorded in or near the INC in monkeys (12). The INC also contains neurons that contribute to neural integration of vertical eye movements. It contains burst-tonic neurons that show a discharge pattern similar to that of vertical oculomotor neurons and receives strong anatomic connections from the vestibular nucleus. The INC is important for holding the eyes in eccentric gaze after a vertical saccade and coordinating eye-head movements in the roll plane. Bilateral destructive INC lesions are known to limit
the range of vertical gaze (10). The main projections from
the INC to ocular motoneurons (in oculomotor and troch­
lear nuclei) and the contralateral INC are through the PC
(13). Therefore, a lesion of the PC may be functionally
a bilateral lesion and affect inputs to motoneurons on both
sides.

REFERENCES
1. Ranalli PJ, Sharpe JA, Fletcher WA. Palsy of upward and downward
saccadic, pursuit, and vestibular movements with a unilateral midbrain
2. Hommel M, Bogousslavsky J. The spectrum of vertical gaze palsy
midbrain infarcts: clinical and neuropathological study. Ann Neurol
paralysis and the rostral interstitial nucleus of the medial longitudinal
electro-oculographic and anatomical analyses of six vascular cases
with declusions about vertical gaze organization in the prefrontal
torsional nystagmus in a unilateral rostral midbrain lesion. Neurology
of reversible inactivation of the primate mesencephalic reticular
formation. II. Hypometric vertical saccades. J Neurophysiol 2000;83:
2285-99.
8. Biiadayani R, Plant GT, Leigh RJ. A hypothetical scheme for the
and selective unilateral infarction of rostral interstitial nucleus of
the medial longitudinal fasciculus (rMLF). J Neurol Neurosurg
10. King WM, Fuchs AF, Magria M. Vertical eye movement-related
responses of neurons in midbrain near interstitial nucleus of Cajal. J
physiology of the primate interstitial nucleus of Cajal I. Efferent
as vertical gaze palsy: value of diffusion-weighted magnetic resonance
imaging. Cerebrovasc Dis 2004;18:37-.
torsional eye movements after uni- and bilateral muscimol in­
activation of the interstitial nucleus of Cajal of the alert monkey. Exp
A Case of Bilateral Simultaneous Sixth Cranial Nerve Palsies Secondary to Diabetes Mellitus

Ayşe Oytun Bayarak, MD, Hacer Erdem Tilki, MD, and Dilek Kasim, MD

Abstract: Ocular motor cranial nerve palsy secondary to diabetes mellitus usually affects one cranial nerve at a time. We report a patient with simultaneous bilateral sixth nerve palsies attributed to diabetes. Although an extremely rare cause of this phenomenon, diabetes may be the explanation after other causes have been excluded.

CASE REPORT

A 71-year-old man was admitted to the hospital because of a 1-month history of painless acute horizontal diplopia. Neuro-ophthalmologic examination was normal except for bilateral impairment of abduction more pronounced on the left (Fig. 1), hypoactive deep tendon reflexes, and distal gradient hypesthesia.

He had a history of surgery for laryngeal cancer 13 years earlier and had been diagnosed with diabetes mellitus 1 month earlier. There was no history of neurologic or cardiac disease, hypertension, cigarette smoking, or alcohol consumption. He had been taking an oral hypoglycemic agent for approximately 1 month. Laboratory examinations included a normal blood count, erythrocyte sedimentation rate, renal and liver function tests, thyroid function tests, and cerebrospinal fluid formula, including cyt centrifuge examination for neoplastic cells. There was an elevated plasma glucose level of 145 mg/dL (normal, 70–110 mg/dL) and HgA1C of 8.5% (normal, 4–6%). A pyridostigmine test for myasthenia gravis was negative. Repetitive nerve stimulation test of the trapezius and orbicularis oculi muscles was normal. Skull x-rays and MRI/magnetic resonance angiography including the neck and head were normal.

Given the normal examinations, we tentatively attributed the ocular motor findings to diabetes mellitus. The patient was prescribed an oral hypoglycemic agent, a controlled diet, and aspirin. Five months later, the ocular motor findings had disappeared (Fig. 2).

DISCUSSION

Ocular motor cranial nerve palsies are common in diabetics, but our case represents an uncommon event in diabetes: bilateral simultaneous nerve palsies. In 1985 (8) and 1966 (9), Rucker reported the distribution and causes of paralysis of the ocular motor nerves in 2,000 patients but did not analyze cases of bilateral involvement. In 1976, Keane (10) analyzed 125 cases of bilateral sixth cranial nerve palsies; none was classified as diabetic. In 1981, Rush and Younge (11) analyzed 1,000 patients with ocular motor cranial nerve palsies and found bilateral involvement of the sixth cranial nerve in 33. None was caused by vascular disorders. In more than half of the cases, the bilateral sixth cranial nerve involvement was associated with head trauma, pontine neoplasm, or aneurysm of the posterior circulation. In that series, 8 patients had bilateral third cranial nerve palsies, 2 of which remained idiopathic. Thirteen patients had bilateral fourth nerve palsies, none from diabetes. In another large study of patients with ocular motor cranial nerve palsies (3), there were 53 cases of bilateral sixth nerve palsies; none was attributed to diabetes. Nine patients had bilateral third nerve palsies, 3 of undetermined cause and none from diabetes. Of the 21 bilateral fourth nerve palsies, none was attributed to diabetes. Considering both studies together (3,11), there were 15 (1.5%) cases with multiple cranial nerve palsies that were attributed to a vascular cause, 3 of them (0.3%) with diabetes. Two of these diabetic cases had asymmetric third and fourth cranial nerve palsies;
At presentation, the patient has reduced abduction bilaterally. The other was not further described. Sergott et al (4) reported two cases of bilateral third and fourth cranial nerve palsies associated with diabetes. In both cases, the ophthalmoplegia resolved completely within a few months. Jay and Nazarian (5) described a patient with bilateral sixth nerve palsy associated with temporal arteritis and diabetes. The cranial neuropathy was attributed to diabetes.

In a 2003 study of 2,229 patients with ocular motor palsy, Trigler et al (6) reported 8 (0.1%) cases with multiple simultaneous palsies attributable to diabetes; 5 were unilateral and 3 were bilateral. The unilateral cases involved third and sixth cranial nerves in all but one case, which had combined third and fourth cranial nerve palsies. The bilateral cases consisted of a right third and left sixth nerve palsy, a right fourth and left sixth nerve palsy, and a right sixth and left fourth cranial nerve palsy. There were no cases of bilateral sixth nerve palsy associated with diabetes. In a study of 137 patients with sixth cranial nerve palsy over...
a period of 15 years, Patel et al (12) found 4 cases of bilateral sixth nerve palsy but none was associated with diabetes. One of the cases was, however, classified in the undetermined group. The etiology of the other 3 cases was not mentioned. In 2005, Keane (7) analyzed 979 cases with multiple optical motor cranial nerve palsies in which 25 cases were attributed to diabetes mellitus but an undocumented number had other potential causes.

The essence of this review is that multiple simultaneous ocular motor cranial palsy is not safely attributed to diabetes. Most cases will eventually be connected to neoplastic or inflammatory disease of the cranial base meninges. A proper workup with high-definition imaging and spinal fluid examination is indicated.

REFERENCES
Homonymous Hemianopia in Stroke

Xiaojun Zhang, MD, Sachin Kedar, MD, Michael J. Lynn, MS, Nancy J. Newman, MD, and Valérie Biousse, MD

Background: Previous reports have suggested that most cases of homonymous hemianopia (HH) are caused by occipital stroke. However, these reports have not always been supported by brain imaging.

Methods: We reviewed the medical records of all patients seen in our unit between 1989 and 2004 who had HH documented by formal perimetry or confrontation visual fields and had undergone brain imaging. HHs were divided into those caused by stroke and by non-stroke conditions. The clinical and visual field characteristics were compared in the two groups.

Results: Among 850 patients with 902 HHs, 629 (69.7%) resulted from stroke, of which 531 (84.4%) were from infarction and 98 (15.6%) from primary intraparenchymal hemorrhage. Non-stroke causes included head trauma (123), brain tumor (102), neurosurgical procedures (22), multiple sclerosis (13), and miscellaneous conditions (13). Occipital lesions most commonly resulted from stroke. The configuration of the HH did not predict where in the retrochiasmal visual pathway the responsible lesion lay.

Conclusions: Ischemic stroke causes most HHs from lesions in the occipital lobe that generally do not produce other neurologic manifestations. The configuration of the HH does not predict the location of the lesion within the retrochiasmal visual pathway.

(J Neuro-Ophthalmol 2006;26:180–183)
Homonymous Hemianopia in Stroke


(suprior and inferior homonymous visual field defects respecting both the vertical and horizontal meridians), partial HH (incomplete HH not respecting the horizontal meridian), HH with macular sparing (homonymous visual field defect sparing the central 5–25° of visual field on the affected side), homonymous scotomatous defects, and homonymous sectoranopia as detailed in another report (15). Congruency was defined as visual field defects identical in size and shape in both eyes. The location of brain lesion was determined based on the head CT or brain MRI report (15).

HHs were divided into two groups according to cause as stroke and non-stroke. The stroke group was further divided into infarction and primary intraparenchymal hemorrhage.

The mean and the standard deviation or the median, 25th percentile, and 75th percentile were obtained for continuous variables; the percentages in the categories along with the standard errors were obtained for categorical variables. The demographic, clinical, and visual field characteristics were compared using a t test or Wilcoxon rank sum test (for continuous variables) and a χ² test (for categorical variables).

RESULTS

Among the 904 HHs included in our study, 629 (69.7%) resulted from stroke and 273 HHs (30.3%) from other conditions, including 123 from head trauma, 102 from brain tumor, 22 from neurosurgical procedures, 13 from multiple sclerosis, 13 from miscellaneous causes, and 2 from undetermined causes (Table 1) (15). Formal visual field testing was obtained in 864 HHs, including 714 GVF,

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<th>TABLE 1. Comparison of clinical features of HH caused by stroke and non-stroke conditions</th>
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*Congruity of visual field defects was not assessed in HH confirmed by confrontation visual field testing only, or in patients who had visual field testing in one eye only.
115 HVF, and 35 with both GVF and HVF testing. Forty HHs were diagnosed by confrontation visual field testing only. Among these 40 HHs, 24 were complete and 16 were incomplete; all 16 were classified as partial HH. The 629 HHs caused by stroke included 531 HHs (84.4%) caused by cerebral infarction and 98 HHs (15.6%) caused by primary intraparenchymal hemorrhage.

As shown in Table 1, HH resulting from stroke occurred in older patients, was more often bilateral and congruous and was more often unaccompanied by other neurologic manifestations (“isolated”) than HH resulting from other causes. Occipital lesions were more common in stroke than in non-stroke cases ($P < 0.0001$).

There were no significant differences in the frequencies of the different configurations of HH in patients with stroke and non-stroke patients. The time from injury to initial visual field test tended to be shorter among stroke cases.

Compared with primary intraparenchymal hemorrhage, infarction occurred more often in older patients ($60 \pm 17$ years vs $50 \pm 18$ years, $P < 0.0001$), was more often responsible for bilateral HH (40 vs 0, $P = 0.001$), and involved the occipital lobes more often relative to optic radiations (56% occipital vs 45% occipital and 30% optic radiations vs 47% optic radiations, respectively, $P < 0.05$).

The configuration of the HH did not reliably predict the location of the responsible lesion within the retrochiasmal visual pathway (Fig. 1).

**DISCUSSION**

This report is the largest series of HHs secondary to stroke. All patients were referred to our service for VF testing either because they had visual complaints or

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**FIG. 1.** Relationship between location of the lesion and configuration of the visual field defect. HH, homonymous hemianopia; HHMS, homonymous hemianopia with macular sparing; HQUAD, homonymous quadrantanopia; HSCOT, homonymous scotomatous defect; PHH, partial homonymous hemianopia.
because the treating physician thought the brain lesion could produce visual impairment. Although most patients were sent to us late, the median time was significantly lower for patients with stroke than for patients with other brain lesions (Table 1). This may reflect better awareness of VF defects in the setting of stroke or possibly better outcome of patients with stroke (whose HH was more often isolated) than of non-stroke patients.

Previous studies have emphasized that most HH is caused by stroke and that most stroke HH is secondary to an occipital infarct (1–3). In these studies, the diagnosis of stroke was based mostly on clinical evaluation and not all patients had undergone brain imaging. Our study, which included neuroimaging in all cases, confirms these results. Previous studies have emphasized that the nature of the lesion may be suggested by the presumed lesion location and the characteristics of the VF defect (1–3). Indeed, macular sparing is considered to result from occipital lesions, specifically occipital infarctions in the distribution of the posterior cerebral artery (1–3,6–8,10,13,14). Our study showed that macular sparing was not only caused by lesions other than stroke, but also resulted from strokes involving the anterior portions of the visual pathways such as the optic tract. Similar findings were observed for homonymous scotomasomes defects. Indeed, it has been previously suggested that one of the causes of macular sparing is incomplete damage to the anterior portions of the retrochiasmal visual pathways (3,16). Homonymous scoto­matous VF defects have been reported in patients who have lesions of the optic tract after pallidotomy for Parkinson disease (17). These VF defects have been attributed to the particular anatomic fiber organization within the optic tract (17–19).

This study confirms that stroke is the commonest cause of HH. The long delay between stroke onset and the recognition of HH suggests that HH is often overlooked in patients with stroke. Because HH can interfere with rehabilitation and is associated with a worse functional outcome in patients with stroke, VF testing should be systematically performed in all patients after a stroke involving the cerebral hemispheres. Finally, HH often precludes driving and should be investigated before allowing patients with stroke to drive.

REFERENCES

Orbital Apex Syndrome From Gnathostomiasis

Pisit Preechawat, MD, Pattama Wongwatthana, MD, Anuchit Poonyathalang, MD, and Araya Chusattayanond, PhD

Abstract: A 16-year-old Thai girl presented with acute unilateral visual loss, proptosis, and ophthalmoparesis. CT demonstrated thickening and enhancement of orbital tissues including the orbital apex. A history of consumption of raw fish, together with the findings of cutaneous migratory swelling and eosinophilia, made the diagnosis of gnathostomiasis likely. Her serum was positive for *Gnathostoma spinigerum* using an immunoblotting technique. Parasites removed from the skin lesions revealed the typical head bulbs with 4 circumferential rows of hooklets and fine cuticular spines on their surface. Treatment with an antihelminthic and systemic corticosteroids led to resolution of orbital inflammation but left a persistent optic neuropathy marked by nerve fiber bundle visual field loss with normal visual acuity. Gnathostomiasis should be suspected in patients with an orbital apex syndrome who live or travel in an endemic area, have eaten raw fish, and develop a migratory skin rash.

(C)Neuro-Ophthalmol 2006;26:184-186)

The orbital apex syndrome results from damage to the third, fourth, or sixth cranial nerves or to the ophthalmic division of trigeminal nerve in association with optic nerve dysfunction. This syndrome includes the clinical findings of unilateral visual loss, proptosis, ptosis, and ophthalmoplegia. The syndrome may be caused by inflammatory, infectious, neoplastic, traumatic, or vascular processes. Infectious diseases reported to cause this syndrome include bacteria, fungi, and spirochetes (1).

Gnathostomiasis is an important food-borne parasitic disease (2). Humans are accidental hosts, acquiring infection by eating third-stage larvae encapsulated in raw freshwater fish. The disease manifests with migratory swelling or creeping eruption accompanied by visceral symptoms related to larval migration. The parasite may migrate to the central nervous system and cause serious effects such as encephalomyelitis and meningitis with long-term neurologic sequelae, even death (3,4). Ocular involvement is rare but has been reported to include the eyelid, conjunctiva, cornea, anterior chamber, vitreous cavity, and retina (5). We report a rare case of a young girl with gnathostomiasis who presented with a progressive orbital apex syndrome, a phenomenon not previously published to our knowledge.

CASE REPORT

A 16-year-old girl presented with a 2-day history of pain, swelling, tearing, and minimal blurring of vision in the left eye. Visual acuity was 20/20 in the right eye and 20/25 in the left eye. There was moderate erythematous eyelid edema with conjunctival hyperemia. Pupillary reactions and ocular motility were normal. A diagnosis of preseptal cellulitis was made and oral dicloxacillin was prescribed.

Twelve hours later, the patient returned to the hospital reporting progressive painful eyelid swelling in her left eye. She now had left proptosis and chemosis and diminished abduction of the left eye. Visual acuity had fallen to 20/200 in the left eye with a relative afferent pupillary defect. Anterior segment and funduscopic examinations were normal in both eyes. The patient was hospitalized with a provisional diagnosis of left orbital cellulitis and started on intravenous vancomycin, ceftriaxone, and metronidazole.

Twelve hours after admission, visual acuity in the left eye had decreased to light perception associated with increased proptosis and chemosis. In addition, left eye abductions had diminished to less than 10% in all directions of gaze. Mydriasis and diminished corneal sensation in the left eye were also noted. The remainder of the patient's neuro-ophthalmologic examination was unremarkable.

Pyrexia was absent. Laboratory results included hemoglobin 12.3 g/dL, white blood count 16,200/mm$^3$ (49% polymorphonuclear cells, 14% lymphocytes, 31% eosinophils, and 6% monocytes), platelets 276,000/mm$^3$, and normal erythrocyte sedimentation rate. CT of the orbits and cavernous sinuses demonstrated diffuse thickening and enhancement along the wall of the left globe, optic nerve, and extraocular muscles (Fig. 1A). Enhancing lesions at the
FIG. 1. A. Postcontrast axial CT at presentation shows left proptosis, an enlarged left optic nerve, and an enhancing mass in the left orbital apex. B. Postcontrast fat-suppressed T1 axial MRI 1 week after starting therapy shows improvement in proptosis and less evidence of orbital inflammation.

left orbital apex and superior orbital fissure were also seen. The paranasal sinuses were normal. There was no evidence of cavernous sinus thrombosis.

The patient recalled an additional history of migratory erythematous swelling in her ankle, waist, back, and neck approximately 1 month earlier. A differential diagnosis of parasitic larva migrans was considered. Intravenous dexamethasone at a dosage of 5 mg four times per day and 400 mg oral albendazole twice per day were initiated.

Cerebrospinal fluid examination revealed no cells, normal protein and sugar, and negative staining for organisms. After 24 hours of corticosteroid therapy, the patient showed remarkable improvement with decreased lid swelling, chemosis, and proptosis, and resolution of pain. Visual acuity had improved to hand movements. During the next several days, the patient showed further improvement of visual acuity and ocular motility. Hemoculture and cerebrospinal fluid culture for bacteria was negative, but serum was positive for *Gnathostoma spinigerum* using an immunoblotting technique (24-kDa diagnostic band). Intravenous antibiotic and dexamethasone were discontinued after 3 days and the patient was treated with 1 mg/kg oral prednisolone per day in addition to albendazole.

By 1 week after treatment, the patient had resolution of proptosis and ocular motility was significantly improved in all directions except for a mild abduction deficit. Visual acuity had improved to 20/50; kinetic perimetry revealed an inferior altitudinal defect. MRI showed marked improvement of periorbital and orbital inflammation (Fig. 1B). The patient was discharged on oral prednisolone and albendazole for 2 weeks.

One week later, visual acuity was 20/40; there was minimal subconjunctival hemorrhage, resolution of conjunctival edema, full ocular motility, and no proptosis. Creeping eruptions were now found on her left leg and right shoulder. Parasites were removed from the lesions and identified microscopically as third-stage larvae of the *Gnathostoma* species. Microscopic study of the parasites revealed a typical head bulb with 4 circumferential rows of hooklets and fine cuticular spines on its surface (Fig. 2).

Visual acuity had recovered to 20/20 by 6 months. Visual field examination showed a persistent inferior arcuate-altitudinal defect that corresponded to supertemporal sectoral pallor of the left optic disc (Fig. 3). Over 2 years of follow-up, she has had no further ocular or neurologic symptoms.

FIG. 2. Microphotograph of the parasite under a coverslip in wet preparation shows the head bulb with 4 rows of hooklets (short arrow) and multiple cuticular spines on the body (long arrow). These features indicate a third-stage larva of the *Gnathostoma* species.
DISCUSSION

Gnathostomiasis, caused by *Gnathostoma spinigerum*, is commonly seen in Thailand and many Asian countries. The clinical symptoms are related to the mechanical disruption caused by third-stage larval migration and the inflammatory reaction provoked by this parasite. Any organ system can be involved, but the most common manifestation of infection is localized, intermittent migratory swelling in skin and subcutaneous tissues. Lid swelling and intraocular parasites are the two most common ocular manifestations (6). The parasite may be found in either the anterior or posterior ocular segment and can cause uveitis, secondary glaucoma, and hemorrhage in the vitreous, retina, or choroid (5). The larva may migrate along the optic nerve before entering the eye, causing orbital inflammation. Sen et al (7) reported a case of orbital inflammation mimicking orbital cellulitis followed by vitreoretinal hemorrhage associated with intraocular gnathostomiasis. Ocular motor nerve palsy, pupillary disorders, visual field defects, and optic neuropathy can be seen but usually develop in patients with central nervous system involvement, including meningitis, encephalitis, and subarachnoid or intracranial hemorrhage (3,4).

The key to diagnosis of gnathostomiasis is recognition of the highly suggestive clinical history. Recurrent migratory swelling and cosinophilia in a patient who is living or has traveled in an endemic area make the diagnosis likely. Many tests are available for the detection of *Gnathostoma* antigens and anti-*Gnathostoma* antibodies (8). The serologic test using the immunoblotting technique with a polypeptide marker weight of 24 kDa of *Gnathostoma spinigerum* has nearly 100% specificity (9,10).

Our case of gnathostomiasis was confirmed with this test and by recovery of the migrating larvae from the patient’s skin lesions.

Albendazole and ivermectin have been used to treat subcutaneous gnathostomiasis but no effective drugs are yet available for the treatment of intracranial or intraocular involvement. Immediate treatment with systemic corticosteroids in our patient improved the condition, resulting in significant recovery.

REFERENCES

Paroxysmal Tonic Downgaze in Two Healthy Infants

Darcy H. Wolsey, MD, MPH and Judith E. A. Warner, MD

Abstract: A 5-month-old boy and 7-month-old girl had episodes of downward eye deviation starting at age 5 months, lasting seconds to minutes, and associated with stiffening of the extremities in one case and grasping, flailing upper extremity movements and retroflexion of the head in the other. There were no other clinical abnormalities. Electroencephalography and MRI were normal. The episodes stopped after 6 to 12 weeks and there have been no sequelae. This idiopathic condition resembles paroxysmal tonic upgaze in infancy. Until further documentation clearly establishes that this phenomenon is benign, evaluation with MRI and electroencephalography is indicated.

(Supranuclear disturbances of gaze have been reported to occur in normal healthy infants. Hoyt (1) described 5 healthy newborns with sustained downgaze while awake. These symptoms all resolved by 6 months with no residual neurologic sequelaes. Ouvrier and Billison (2) described older infants with upward deviation of the eyes that occurred for brief episodes, which they labeled “paroxysmal tonic upgaze” (PTU). Most of these cases also resolved without clinical consequences. We present two cases of brief episodes of downgaze in healthy infants that appear to have features in common with PTU.)

CASE REPORTS

Case #1
A 5-month-old healthy boy presented with paroxysmal tonic downgaze. The patient was born at full term and had normal development. The spells started 7 days before presentation, each episode lasting between 10 seconds and 1 minute. He had many spells per day that seemed to occur more frequently when he was supine. The longer spells were associated with stiffening of upper and lower extremities without any impairment in consciousness. He was diagnosed with an ear infection at the time the spells started. The spells were witnessed by a primary care physician and an emergency room physician. The physicians and his mother described the spells as consisting of extreme downgaze with some adduction of both eyes.

Ophthalmologic examination disclosed that he fixed and followed equally with each eye. He had normal ocular alignment and full extraocular movements without nystagmus. All other aspects of the examination were unremarkable. The patient had no spells during examination despite lying supine for 1 hour. On one occasion, when the left eye was occluded, the eyes crossed and depressed briefly. This was reportedly similar to the episodes but much briefer and less extreme. Neurologic examination demonstrated a bright, alert, babbling child in excellent humor. He had normal muscle tone and strength, and all four extremities moved spontaneously. Deep tendon reflexes were normal.

Evaluation included a normal electroencephalogram (EEG), brain CT, and brain MRI. The manifestations resolved within 6 weeks of onset. He did not develop any neurologic problems in the subsequent 12 months.

Case #2
A 7-month-old healthy girl born at full term after a normal pregnancy and delivery presented with paroxysmal tonic downgaze (Fig. 1). These manifestations started at age 5 months with episodes of downgaze lasting approximately 10 seconds. Associated movements included grasping and flailing of the arms and throwing back of the head. The spells became longer and more frequent 3 weeks after they started, lasting 30 to 60 seconds, with several episodes occurring over the course of 5 minutes. The episodes began decreasing in frequency 2 weeks later and resolved within 3 months. There was no associated illness or vaccination.

Our ophthalmologic examination disclosed that she fixed and followed equally with each eye and with both
FIG. 1. Case #2 is a 7-month-old girl with extreme downgaze. The downgaze occurred in episodes that initially lasted 10 seconds but later increased in duration to 60 seconds. The episodes resolved spontaneously.

eyes together. All other aspects of the ophthalmologic examination were also normal. Neurologic examination showed normal strength and tone of all extremities, normal deep tendon reflexes, and no ataxia. Brain MRI was normal. Because her ophthalmologic manifestations appeared to be resolving, no EEG was performed. She had developed no neurologic abnormalities after 18 months of follow up.

DISCUSSION

The two patients we describe had an episodic downward gaze disturbance that could be called paroxysmal tonic downgaze. The infants displayed other abnormal body movements during the episodes, but their EEG and brain imaging were normal and the episodes resolved without the appearance of any abnormalities over a prolonged follow up. Episodes of tonic downward deviation have been previously reported (1,3–6), but our cases do not precisely fit these descriptions.

There have been three reported syndromes of downgaze in infancy. Hoyt (1) examined 242 healthy neonates and described 5 with a downgaze abnormality. These 5 patients had persistent tonic downward deviation of the eyes while awake and normal oculocephalic responses and a normal Bell phenomenon while asleep. The downgaze had disappeared by 6 months of age without any clinical sequelae. Walsh and Hoyt (3) also described two infants with similar downgaze episodes, but details in their report are sparse. Our two patients with downward deviation of the eyes were older at the time of onset of the gaze abnormality. Also, our patients' downgaze occurred in brief episodes lasting seconds, whereas Hoyt's cases had downgaze during all waking hours.

Kleiman et al (4) described a second syndrome of downward gaze deviation lasting seconds and occurring 2 to 3 months after birth in five preterm infants (22–28 weeks gestation). These episodes also resolved and the infants appeared to be developing normally. Very similar downgaze episodes have been described in older infants (age 2–8 months) with severe developmental disabilities (5). Although the episodes are very similar to those of our patients, they occurred in preterm infants or in infants with severe neurologic disturbances.

A third paroxysmal downward eye deviation in infancy is the "eye-popping" reflex (6). This phenomenon is a short-lived (3–10 seconds) downward deviation of the eyes associated with dramatic lid retraction occurring reliably after sudden change of illumination from light to dark. This reflex was found in 29% of normal infants in the neonatal period increasing to a peak of 78% in at 14 to 18 weeks of age. Our patients did not have lid retraction or episodes triggered by sudden exposure to darkness.

Our two cases of downgaze spells do not fit these previously described downgaze disorders. They are, however, similar to the upward deviations first described by Ouvrier and Billson in 1988 (2) as "paroxysmal tonic upgaze." Paroxysmal tonic upgaze of childhood is characterized by sustained conjugate upward deviation of the eyes with downbeating saccades in attempted downgaze (2,7). Neurologic, ophthalmic, and radiologic evaluations were all normal and there was no evidence of seizure activity on EEG (2,8). Onset has been described in children age 1 week to 7 years but most often before age 1 (2,7–9). It often occurs shortly after illness or vaccination. Symptoms are relieved by sleep (9).

Most cases of PTU resolve without clinical consequences, but neurologic abnormalities have been described, including ataxia, developmental delay, amblyopia, and strabismus (7–9). In 2005, Ouvrier (9) reviewed 45 cases of PTU from personal experience and from the literature and found 50% had mild cognitive or language problems, approximately 25% had residual ataxia, and approximately 20% to 25% had other ocular motility problems such as strabismus or nystagmus. Our two cases have had normal ocular and neurologic development since resolution of the symptoms. More cases of paroxysmal tonic downgaze will need to be followed to determine if any will have subsequent neurologic abnormalities as seen with some of the PTU cases.

The pathogenesis of these transient gaze disturbances is not understood. Some hypothesize that the transient deviation may be the result of immature myelination of the corticomesencephalic vertical gaze pathways (3). The transient nature of the disorders, especially in older infants, may result from temporary failure of cortical compensation when a stressor such as illness is present (6,9). Because downward deviation of the eyes has been associated with hydrocephalus, coma of various causes, and seizures (5), MRI scanning and EEG are indicated in the investigation of paroxysmal tonic gaze deviations in infants.
REFERENCES


Optic Neuropathy and Sixth Cranial Nerve Palsy Caused by Compression From a Dolichoectatic Basilar Artery

Jack Yu-Shih Lin, MD, Szu-Yuan Lin, MD, Joseph I-Chieh Wu, MD, and I-Hua Wang, MD

Abstract:
A 53-year-old man with progressive visual loss in the right eye and diplopia manifested dysfunction of the right optic nerve and the right sixth cranial nerve. MRI revealed a markedly enlarged and tortuous basilar artery, its proximal portion compressing the right sixth cranial nerve at the exit from the pons and its distal portion elevating and compressing the right optic nerve. This is the first report of optic neuropathy and sixth cranial nerve palsy caused by a dolichoectatic basilar artery.


A 53-year-old man presented with progressive loss of vision in the right eye and recent diplopia. His medical history was significant for hypertension and two strokes. Best-corrected visual acuity was finger counting in the right eye and 20/60 in the left eye. The patient identified zero of 13 Ishihara plates with the right eye and 13 of 13 plates with the left eye. Visual field examination revealed a dense field defect in the right eye and peripheral constriction and generalized depression in the left eye. There were no ocular adnexal abnormalities. Pupils were equal in size but a relative afferent pupillary defect was present in the right eye. Right abduction was 60% of normal. He had a right esotropia of 40 prism diopters. Slit lamp biomicroscopy revealed moderate cortical nuclear cataract in the left eye consistent with 20/60 visual acuity. Funduscopy revealed bilateral retinal arterial narrowing and deflections of veins at the arteriovenous crossing consistent with grade 2 hypertensive retinopathy. A diffusely pale disc in the right eye and a normal optic disc in the left eye were also found.
MRI revealed a tortuous vertebrobasilar artery dilated up to 8 mm in diameter, its proximal dolichoectatic portion compressing the right pons (Fig. 1) and its distal portion compressing and upwardly displacing the right optic nerve (Fig. 1).

Rigorous control of hypertension was recommended. On a follow-up visit 18 months later, there were no significant changes in his vision or ocular motility.

Vertebrobasilar dolichoectasia refers to the elongation and distension of the vertebrobasilar system. Ectasia is diagnosed when the diameter of the basilar artery is greater than 4.5 mm (1). It can lead to multiple neurologic dysfunctions by compression of adjacent tissue, including the cranial nerves, with the trigeminal and facial nerves being the most frequently affected (2). Sixth cranial nerve palsy, either isolated or combined with other neurologic deficits, has been reported (3,4). Compression of the visual pathway is rare with only one reported case (5). To our knowledge, the combination of sixth cranial nerve palsy and optic neuropathy has not been reported. It is of interest that despite dolichoectasia of such magnitude, our patient had no other neurologic deficits.

REFERENCES
Regression of Bilateral Optic Disc Edema After Discontinuation of Amiodarone

Roman Shinder, MD, Larry P. Frohman, MD, and Roger E. Turbin, MD, FACS

Abstract: A 54-year-old non-obese woman treated with amiodarone reported blurred vision and had bilateral optic disc edema with relative preservation of visual function. Neurologic examination, brain imaging, and lumbar puncture opening pressures were normal, effectively ruling out increased intracranial pressure. Amiodarone was discontinued and the optic disc edema completely resolved over 15 months. In the absence of alternative explanations for the optic disc findings, amiodarone toxicity is suggested.

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A 54-year-old woman with no ocular history reported the recent onset of blurred vision and floaters in the right eye without headaches. She had begun amiodarone 600 mg per day 6 months earlier for atrial fibrillation in the setting of myocardial infarction and had required a pacemaker and placement of a mechanical valve for mitral valve stenosis 8 months earlier. The patient’s other medications included warfarin and zolpidem.

Her height was 5 feet 5 inches and she weighed 150 lbs. General physical and neurologic examination was normal without heart failure or cor pulmonale.

Visual acuity was 20/15 in both eyes and Ishihara color vision testing was normal. The pupils were equal in size, briskly reactive to light, and without afferent defect. Slit lamp examination were normal with the exception of mild corneal verticillata. Funduscopic examination showed bilateral optic disc edema (Fig. 1) confirmed on optical coherence tomography (OCT) (Fig. 2). Automated static perimetry revealed visual fields with mild blind spot enlargement and minimal peripheral constriction in both eyes (Fig. 3).
Optic Disc Edema in a Patient Treated with Amiodarone


FIG. 2. Optical coherence tomography (OCT) of the right and left optic nerves at presentation shows optic disc edema with the plane of the image through the horizontal nasotemporal axis. OCT scans show gradual resolution of nerve fiber layer thickening over 15 months. (The black line represents the tomographic plot of the actual nerve fiber layer elevation plotted against age-matched normals [in green] and abnormals [red] at $P < 0.05$. The early scans show so much optic disc elevation that the plots are mostly off the upper end of the available scale.)
A high-resolution CT scan of the head and orbits with contrast was normal. The presence of a pacemaker prevented MR scanning. A lumbar puncture performed at presentation and repeated 2.5 months into her course revealed normal opening pressures of 160 mm and 150 mm of water. Cerebrospinal fluid constituents, including cell count and cytology, were normal.

The optic disc edema was attributed to amiodarone toxicity and this medication was promptly discontinued. Over the next 15 months, the optic disc edema gradually resolved as shown by serial optic disc photographs and OCT (Figs. 1 and 2). Visual acuity and color vision testing remained normal throughout the course and visual fields showed continued improvement over the ensuing 7 months (Fig. 4).

This patient developed bilateral optic disc edema without substantial visual loss mimicking papilledema. However, investigation for increased intracranial pressure was negative. Because we could discover no alternative explanation, we blamed the ophthalmic findings on amiodarone toxicity. Although cited as occurring in up to 1% to 2% of patients taking the medication (1), the true incidence of amiodarone optic neuropathy and the mechanism by which the drug causes optic neuropathy are incompletely characterized. Furthermore, the visual complaints in patients with amiodarone optic neuropathy may be insidious or difficult to distinguish from other forms of optic neuropathy affecting a similar patient population with cardiovascular risk factors. Chronicity, bilateral presentation, and progression over several months favor drug toxicity. The clinical severity of this drug-related optic neuropathy has been characterized as milder than that described in anterior ischemic optic neuropathy, and patients may have preserved visual function (2,3). The optic disc swelling is typically bilateral and symmetric and can be quite marked (4). Visual field defects may be mild and reversible or severe and permanent (5). Optic disc swelling usually resolves many months after discontinuation of amiodarone (6,7), as occurred in our patient.

REFERENCES

Monocular Temporal Hemianopia With Septo-Optic Dysplasia

Dain B. Brooks, MD and Prem S. Subramanian, MD, PhD

**Fig. 1.** A. "Bowtie" optic disc pallor and small-diameter optic disc in the right eye and normal optic disc in the left eye. B. Visual fields show temporal hemianopia in the right eye and a normal result in the left eye. C. Postcontrast T1 coronal MRI shows a thin right optic nerve just anterior to the optic chiasm, absent septum pellucidum, and normal-appearing pituitary gland (left); midorbital view shows a thin right optic nerve (right).
Abstract: A 26-year-old woman displayed a monocular temporal hemianopic defect together with an ipsilateral afferent pupillary defect and bowtie optic nerve hypoplasia. MRI revealed a thin right optic nerve, an asymmetrically thinned chiasm, and an absent septum pellucidum. Monocular temporal visual field loss from organic lesions is quite rare but has been reported in conjunction with compressive lesions at the optic nerve–optic chiasm junction. This is the first report to demonstrate this visual field defect together with bowtie optic nerve hypoplasia. (J Neuro-Ophthalmol 2006:26:195–196)

A 26-year-old black woman was referred to the neuro-ophthalmology service after she described bumping into things on her right side for the last 18 months. She also believed that the vision on the right side was diminished. She had a history of childhood esotropia with amblyopia in the right eye and had been treated with patching of the left eye.

During the same time period, she reported the onset of systemic hypertension and low back pain. She denied recent trauma or serious illnesses requiring hospitalization.

Visual acuity was 20/70 in the right eye and 20/20 in the left eye. There was a right afferent pupillary defect (APD) and a small-diameter optic disc with a “bowtie” pattern of pallor (Fig. 1A). A right temporal visual field defect respecting the vertical midline was noted by finger confrontation and confirmed on automated perimetry (Fig. 1B). Brain MRI disclosed a small-diameter right optic nerve and absence of the septum pellucidum (Fig. 1C). Pituitary function was normal.

A monocular temporal hemifield deficit may result from optic nerve damage just anterior to the optic chiasm. In this variant of the anterior chiasmal syndrome (1), the damage often (but not always) produces an APD on the side of the lesion and a visual field defect that variably respects the vertical midline (2,3). “Wilbrand’s knee” need not exist for this type of nerve fiber damage to occur (4). In a series of 24 patients, selective compression of the nasal crossing fibers from one optic nerve by suprasellar or juxtasellar lesions identified on imaging, why were the nasal nerve fibers selectively damaged? An incomplete midline cleavage defect might be expected to damage only the crossing fibers of one eye, although the marked asymmetry defies easy explanation. Monocular temporal hemianopia with absent septum pellucidum has been reported previously (8) but the features notably differ. Specifically, we found optic nerve hypoplasia with “bowtie” nerve fiber loss in lieu of apparent nasal agenesis of the optic nerve; the potential association of such markedly different patterns of optic nerve hypoplasia with apparent midline dysgenesis is unexpected. We further demonstrate that the abnormality of the optic nerve is visible both intraorbitally and intracranially. Finally, our case demonstrates that this condition may go unrecognized until adulthood with apparent new onset of symptoms.

REFERENCES
PHOTO ESSAY

Subretinal Hemorrhage From a Peripapillary Choroidal Neovascular Membrane in Papilledema Caused by Idiopathic Intracranial Hypertension

Busaba Sathornsumetee, MD, Adam Webb, MD, Donna L. Hill, MD, Nancy J. Newman, MD, and Valérie Biousse, MD

FIG. 1. A. One week after initial presentation, chronic optic disc edema is evident in both eyes as well as a subretinal hemorrhage surrounding the left optic disc. B. Two months after left optic nerve sheath fenestration, optic disc edema has lessened in both eyes allowing better visualization of a peripapillary whitish elevation in the left eye.

Abstract: A 42-year-old man with idiopathic intracranial hypertension and chronic papilledema had severe visual loss in his left eye caused by subretinal bleeding from a peripapillary choroidal neovascular membrane (CNVM). After optic nerve sheath fenestration in his left eye, the papilledema improved, allowing improved visualization of the CNVM. Visual function did not improve after the surgery. CNVM can complicate chronic papilledema and account for sudden worsening of vision. The appropriate management of this type of CNVM is unresolved.
A 42-year-old man presented with a 1-month history of painless vision loss in both eyes. There were no other neurologic symptoms.

Blood pressure was normal. Best-corrected visual acuity was 20/30 in the right eye and 20/300 in the left eye without relative afferent pupillary defect (RAPD). Ophthalmoscopic examination showed bilateral disc edema. Neurologic examination was otherwise normal.

Complete blood cell count, metabolic profile, erythrocyte sedimentation rate, and rapid plasma reagin were normal. Brain and orbit MRI with MRV was normal. Lumbar puncture revealed an opening pressure of 30 cm H2O and a normal formula.

One week later, visual acuity was 20/30 in the right eye and 20/100 in the left eye, again without RAPD. Ophthalmoscopic examination showed persistent bilateral disc edema and a peripapillary temporal subretinal hemorrhage in the left eye extending to the fovea. A gray-white opacity present on the temporal edge of the optic disc merged with the optic disc edema (Fig. 1A). Humphrey visual fields revealed an enlarged blind spot in the right eye with constriction, and an enlarged blind spot in the left eye with nasal depression.

He was treated with acetazolamide, which he did not tolerate. Therefore, he underwent an uncomplicated optic nerve sheath fenestration in the left eye.

Two months later, visual function had not improved in the left eye. He continued to deny any headache or associated symptoms. Visual acuity was 20/20 in the right eye and counting fingers at 3 feet in the left eye. There was a 0.6 log unit left RAPD. The visual field deficit was stable in the right eye and had worsened in the left eye. Ophthalmoscopic examination now showed a more obvious temporal peripapillary gray-white subretinal opacity and hemorrhage (Fig. 1B). The gray-white opacity took up intravenous fluorescein, confirming that it was a choroidal neovascular membrane (Fig. 2). The subretinal hemorrhage blocked choroidal transmission.

The patient refused further treatment. Nine months later, his visual function was unchanged.

This case is presented to highlight the fact that a peripapillary choroidal neovascular membrane may be a cause of sudden visual loss in the setting of papilledema. The membrane was not initially obvious; it became more evident as disc edema resolved after optic nerve sheath fenestration.

Peripapillary choroidal neovascular membrane is an exceedingly rare complication of chronic papilledema. Fewer than 15 cases have been reported (1–9). The presumed pathogenesis is pressure deformity of the border of Bruch’s membrane at the level of the optic nerve head creating a discontinuity of the normal anatomic apposition of the chorioretinal layers. This anatomic dehiscence, coupled with hypoxia created by axonal swelling, may promote angiogenesis leading to the formation of a neovascular membrane (4).

These peripapillary choroidal neovascular membranes have been treated with laser, photodynamic therapy, or surgery to prevent subfoveal extension (1,4,7,9). This treatment has resulted in regression of the membrane or improvement of visual acuity in approximately 50% of cases. Others have suggested that these membranes may not need treatment because they have a good prognosis and may even spontaneously regress once papilledema has improved (2,5,6,8,9). Among the 7 patients left untreated (2,5,6,8,9), 5 patients had a good visual outcome (2,5,6,9), 1 patient had extension of the choroidal neovascular membrane toward the fovea (9), and 1 patient with a subfoveal neovascular membrane had worsening of vision (8). None had recurrent hemorrhage.

Although the optic nerve sheath fenestration resulted in dramatic improvement of the papilledema in our patient, the choroidal neovascular membrane had not resolved 9 months later.

REFERENCES


New Concepts in the Diagnosis and Management of Optic Nerve Sheath Meningioma

Neil R. Miller, MD

Abstract: Optic nerve sheath meningiomas are by far the most common tumors of the optic nerve sheath. The diagnosis can be suspected in most cases from clinical findings and supported by the results of neuroimaging, obviating tissue biopsy in the majority of cases. Observation may be appropriate in patients with mild or no visual deficit or in whom visual loss is not progressing, whereas stereotactic fractionated radiation therapy has been demonstrated to improve or stabilize vision in progressive or advanced cases. Attempts at surgical excision, and even biopsy, of optic nerve sheath meningiomas are associated with a high risk of blindness and should be reserved for the rare case of an anteriorly located, primarily exophytic tumor with focal involvement of the dural sheath.

(J Neuro-Ophthalmol 2006;26:200–208)
Neil Richard Miller, MD, was born in Wichita Falls, TX and grew up in Omaha, NE. He graduated from Harvard College in 1967 with a magna cum laude in biochemistry. He completed medical school, medical internship, and ophthalmology residency at Johns Hopkins University, and after a neuro-ophthalmology fellowship at the University of California-San Francisco from 1975 to 1976, returned to the Wilmer Eye Institute at Johns Hopkins University, rising through the academic ranks to become the Frank B. Walsh Professor of Neuro-ophthalmology in 1987.

Widely regarded as a scholar’s scholar, he is generally the last word on virtually any subject in the field of neuro-ophthalmology. His academic output is unrivaled. The author of over 360 peer-reviewed journal articles and 60 book chapters, he is also the co-author of eight books, among them the biblical *Walsh & Hoyt’s Clinical Neuro-Ophthalmology*, now in its 6th edition. William F. Hoyt, MD, who had largely written the 3rd edition, selected Dr. Miller as the author of the 4th edition. Dr. Miller has trained some of the finest neuro-ophthalmologists in the world, and has been president of the North American Neuro-ophthalmology Society (NANOS) (2000-2002) and the International Neuro-ophthalmology Society (INOS) (1980-1982, 1990-1992).

Rarely, the tumor infiltrates the dura and spreads beyond the confines of the nerve to infiltrate adjacent orbital structures, including fat, extraocular muscles, and bone. When the tumor spreads to adjacent bone, it may enter the Haversian canal system, inciting hyperostosis and bone proliferation (5).

In a meta-analysis by Dutton in 1992 (1), the mean age at presentation for ONSMs was 41 years (range, 3–80 years) with women being affected more frequently than men (3:2). Patients with neurofibromatosis had a higher incidence of ONSM compared with the general population. Almost all cases (95%) were unilateral. The majority of ONSMs were intraorbital with 8% confined to the optic canal. Interestingly, canalicular meningiomas had a higher incidence of bilaterality (38%) than ONSMs within the orbit. In a subsequent series reported by Saeed et al in 2003 (6), half of the patients with bilateral ONSMs had tumors along the planum sphenoidale in continuity with the lesions in both optic canals. Thus, it would appear that some cases of apparently bilateral ONSMs are truly bilateral, whereas others represent either the spread of a planum sphenoidale meningioma to both optic canals or of a unilateral ONSM across the planum to the contralateral optic canal.

Approximately 4% to 7% of ONSMs occur in childhood (1,2). Unlike ONSMs that occur in adults, there is no gender predilection and they are often associated with neurofibromatosis type 2. In addition, ONSMs in children often behave in a more aggressive fashion characterized by faster growth and more frequent intracranial and bilateral involvement than occurs in adults (6).

CLINICAL MANIFESTATIONS

The majority of ONSMs present with a slowly progressive optic neuropathy characterized by a variable loss of visual acuity (1,6–8). In the Dutton study (1), 45% of patients had a visual acuity of 20/40 or better, whereas fewer than 25% had counting fingers or worse. Even patients who do not have significant reduction in visual acuity often have disturbances of color vision and visual field. Less common symptoms in patients with ONSMs include periocular or retrobulbar pain or discomfort, double vision, and transient visual obscurations (1,6–8). The obscurations of vision are almost always associated with optic disc swelling and in some cases are exacerbated or induced by eye movement.

Almost all patients with a unilateral ONSM have an ipsilateral relative afferent pupillary defect and most have optic disc swelling without peripapillary hemorrhages or soft or hard exudates (1,6–8). Other ophthalmoscopic findings include macular swelling contiguous with a swollen optic disc, choroidal folds, and acquired retinochoroidal shunt vessels (Fig. 2). Indeed, the triad of visual loss, optic disc pallor, and retinochoroidal shunts is almost pathognomonic for ONSM, although this triad tends to occur relatively late in the course of the disorder (9). Orbital signs such as proptosis are present in 30% to 65% of patients with ONSMs depending on the series (1,6). Mechanical restriction of ocular motility is found in 39% of patients (6) but is usually asymptomatic.

IMAGING

The diagnosis of an ONSM may be made by a variety of imaging studies, most often high-resolution CT scanning (10), thin-section MRI (11), or ultrasonography (12). These studies generally obviate the need for tissue biopsy in most cases, making an early diagnosis possible without potentially damaging the optic nerve during surgery. Nevertheless, metastatic infiltration of the optic nerve and optic nerve sheath (13,14), as well as lymphoma (15) and inflammatory lesions such as sarcoid (16,17) or sclerosing orbital inflammation (18), may mimic ONSMs, and these should be considered in the differential diagnosis of a patient with a presumed ONSM.

ONSMs have 3 main morphologic patterns on imaging: tubular, fusiform, and globular (6). CT typically shows enlargement of the optic nerve with an increased density peripherally and decreased density centrally (the "tram-track" sign) (19). These changes are particularly well seen after intravenous injection of iodinated contrast material (Fig. 3). In addition, in some cases of ONSM, calcifications surrounding the nerve are present on CT, although they may be masked by contrast enhancement and thus are best identified on precontrast soft tissue and bone-windowed images (10). The presence of such calcifications is thought to indicate slow growth (6).

MRI provides somewhat better detail of ONSMs than does CT (11). In particular, the soft tissue component of the tumor is readily visible, particularly when T1 images are viewed in contrast-enhanced, fat-saturated images. The appearance of the optic nerve on enhanced coronal MRI images is most often that of a hypodense area (the optic nerve) surrounded by an enhancing thin, fusiform, or globular ring of tissue (the tumor) (Figs. 4–6). Careful

FIG. 2. Fundus of a patient with a left optic nerve sheath meningioma shows slightly swollen, superiorly pale optic disc with multiple retinochoroidal shunt vessels (arrows).

FIG. 3. Precontrast axial CT of a presumed left optic nerve sheath meningioma demonstrates a hyperintense left optic nerve sheath with central lucency corresponding to the nerve (the "tram-track" sign).
examination discloses that, rather than having a perfectly smooth outline, all forms of ONSMs have very fine extensions into the orbital fat (Fig. 5). MRI also provides sufficient tissue detail that one can assess intracranial extension (1,6,11).

Ultrasound of the orbit can also be helpful in the diagnosis of an ONSM. Echographic evaluation of an ONSM characteristically shows an enlargement in the diameter of the nerve with predominantly medium-to-high reflectivity and an irregular acoustic structure. There may be shadowing from internal calcification (1). In many cases, a 30° test reveals solid thickening of the nerve, whereas in others, the tumor is located more posteriorly and the anterior enlargement of the nerve is the result of cerebrospinal fluid trapped by the tumor (12).

In rare cases, small tumors located within the optic canal are impossible to detect using currently available neuroimaging procedures. Such lesions are usually discovered during exploratory craniotomy and unroofing of the canal. The lesions may be suspected, however, in any patient with slowly progressive, unilateral loss of vision associated with signs of optic neuropathy. In addition, the presence of enlarged, aerated, posterior ethmoid and sphenoid sinuses, a condition known as pneumosinus dilatans, is believed by some authors to be pathognomonic of an ONSM even when such lesions are not obvious on neuroimaging (20).

FIG. 5. Fusiform optic nerve sheath meningioma. A. Precontrast T1 axial MRI shows fusiform mass surrounding the right optic nerve. The nerve can just barely be identified coursing through the mass. B. Postcontrast T1 axial fat-suppressed MRI shows the enhancing nature of the mass, which surrounds the relatively hypointense optic nerve.

HISTOLOGY

Two histologic patterns are seen in ONSMs (21). In the meningotheial or syncytial pattern, polygonal cells are arranged in sheets separated by vascular trabecula. Mitoses are uncommon. In the transitional pattern, spindle or oval cells are arranged in whorls. Psammoma bodies are common in this form and develop from hyalinization and deposition of calcium salts in the degenerated centers of the whorls.

MANAGEMENT

Biopsy

The imaging characteristics of ONSMs are so typical that rarely is biopsy required for diagnosis. As noted previously, however, some processes such as sarcoidosis may produce an appearance that mimics that of an ONSM. Thus, under certain circumstances such as an atypical clinical course characterized by sudden or rapidly progressive visual loss, it may be appropriate to biopsy the nerve. In such cases, one can reach the nerve from the lateral or medial orbital side or, if the lesion is in the optic canal, from an intracranial or transnasal endoscopic approach. The biopsy should be limited to the dural sheath and subdural tissue without violating the nerve itself.

Surgery

Traditionally, ONSMs have either been observed without intervention or treated by excision of the tumor.
FIG. 6. Globular optic nerve sheath meningioma. Post-contrast T1 sagittal MRI shows a well-circumscribed globular lesion that appears to be adjacent to the optic nerve. Note some enhancement of the optic nerve sheath beneath the tumor. The lesion was thought to be a cavernous hemangioma, but surgery disclosed a meningioma. The lesion was removed without loss of vision, which has remained normal for several years. (Photo courtesy of S. Pitz.)

along with the nerve because of concern for intracranial extension. In such cases, the patient is blind after surgery, and disturbances of eyelid function and eye movements are often present (1). Attempts to excise these tumors while keeping the optic nerve itself intact are usually unsuccessful, and most patients are blind in the eye after such surgery (2,6,22–24). The only exceptions are ONSMs that are primarily extradural (1). In such cases, the bulk of the tumor can be excised (25), although rarely if ever can the entire tumor be removed, because at least some of the tumor remains behind in the subdural or subarachnoid space surrounding the nerve (1,6). In other cases, particularly those with acute visual loss, some authors recommend opening the optic nerve sheath to decompress the nerve (6,26). I believe that this procedure should be used only if followed by fractionated radiation therapy (see subsequently). Otherwise, the visual improvement is only temporary and tumor may subsequently spread throughout the orbit.

Medication

To date, trials of medical therapy for ONSM have not been successful. Because meningioma cells often express a variety of hormone receptors, most commonly for estrogen or progesterone (27), it might be expected that treatment with estrogen or progesterone antagonists would result in destruction of the tumor or at least reduction in its size and extent, but this does not seem to be the case. Similarly, although hydroxyurea has been said to be helpful in some cases of intracranial meningioma, I am aware of only one case report in which the treatment of an ONSM with hydroxyurea resulted in visual improvement (28).

Radiation

Radiotherapy for ONSM was initially used only as an adjuvant to surgery because meningiomas in general were once considered to be completely radioresistant. In 1981, however, Smith et al (29) reported the successful treatment of 5 patients with ONSMs using conventional fractionated radiotherapy. These authors documented improvement in visual acuity in 2 patients, an improvement in the visual field in 3, and regression of retinochoroidal shunt vessels in 2 patients. Kennerdell et al (23) subsequently treated 6 patients with fractionated radiation therapy and documented improvement in visual acuity and visual fields in 5 and stabilization in 1 patient. No complications were observed during a follow-up period that ranged from 3 to 7 years.

In 2002, Turbin et al (30) reported a retrospective series of 64 patients with ONSMs who had been managed with observation alone, surgery, surgery with radiation, or radiation alone. The study included patients from the original report of Kennerdell et al (23). The follow-up in this study ranged from 51 months to 516 months with a mean follow-up of 150 months. The authors (30) concluded that treatment with radiation alone resulted in the best long-term visual outcome, although approximately one-third of patients treated in this fashion developed complications from the radiation, including radiation retinopathy, retinal vascular occlusion, persistent iritis, and temporal lobe atrophy. The study did not describe which radiation technique was used, but given the era during which the study was conducted and the length of time the patients were followed, it is likely that the majority of the patients were treated with conventional rather than conformal or three-dimensional (stereotactic) treatment techniques that maximize dose to the tumor and minimize collateral damage (see “Management” subsequently).

The major concern with radiotherapy for ONSMs is late toxicity. Not only can radiation damage the optic nerve itself, but adjacent tissues can also be damaged, including the retina, pituitary gland, and the white matter tracts of the brain (31). Retinal injury has been described with exposures of more than 50 Gy (32,33), but coexistence of diabetes mellitus may lower the threshold for retinal or optic nerve damage to 45 Gy (33,34). Late pituitary dysfunction is a rare complication of radiation as is small-vessel injury in the anterior temporal lobe after irradiation of ONSMs that extend intracranially (23,35).

The threshold for radiation damage to the optic nerve, optic chiasm, or both has been estimated to be 8 to 10 Gy for a single dose (34). Because lower doses of radiation have an uncertain effect on benign tumors such as ONSMs, and a large, single dose of radiation is associated with
a high risk of tissue damage (36), single-dose stereotactic radiosurgery is not widely used to treat ONSMs (37,38). Stereotactic fractionated radiotherapy (SFR) appears to offer the potential for delivering a sufficient amount of radiation to an ONSM in a manner more focused than that of conventional fractionated radiation therapy; thus minimizing the complications from exposure of the surrounding tissue to high doses of radiation.

SFR requires complex planning, which is facilitated by sophisticated software and three-dimensional imaging. The pretreatment imaging (CT and/or MRI) and radiation delivery require the patient to be repeatedly immobilized, although the newest linear accelerator (LINAC) units such as the CyberKnife (Accuray Incorporated, Sunnyvale, CA) use a tracking system that eliminates the need for rigid immobilization during the treatment phase. Unlike conventional radiation therapy, the LINAC system delivers the radiation in noncoplanar fields that take into account the characteristics of the surrounding tissue. Every beam is size-adjusted and shape-adjusted by different devices, microleaf collimators being the most advanced way of achieving a high degree of conformality to the tumor, thus minimizing irradiation of the surrounding tissue (39).

In 1996, the first case report (40) documented improvement of vision after conformal irradiation of ONSM. Since then, at least 7 published series have documented improvement or stabilization of vision after SFR (6,35,41-45). These series are discussed in detail below.

**PREFERRED TREATMENT OPTIONS**

**Observation**

The natural history of ONSMs is loss of visual acuity that progresses slowly in most patients over many years (6-8,46). ONSMs are not associated with any mortality or neurologic morbidity and they do not metastasize. Thus, their only adverse effect is on visual sensory function. In a series reported by Narayan et al (42), 6 of the 7 patients with initial visual acuity of 20/40 or better who were followed without intervention had nearly complete loss of vision over an average duration of 9 years. Nevertheless, observation is appropriate if there is no significant visual dysfunction, no significant progression of visual loss, or no significant intracranial extension of the tumor. In such cases, a clinical examination, including assessment of visual acuity, color vision, and visual fields, should be conducted twice a year for 2 to 3 years and then once a year if the patient’s visual function has remained stable. Patients should be counseled to contact their physician if they note any visual loss in the interim. Neuroimaging at 6-month intervals is appropriate for the first 1 to 2 years, then once a year for 2 to 3 years, and then every 3 to 4 years assuming the clinical examination is stable (47,48). Because younger patients are more likely to have larger or more rapidly developing tumors, children and young adults with presumed ONSMs should be followed clinically and with neuroimaging at more frequent intervals.

**Stereotactic Fractionated Radiotherapy**

Several published series (6,35,41,42-45) describe SFR as a primary treatment option for ONSMs (Table 1). Overall disease control in 70 patients was 94.3%. Improvement of visual function occurred within the first 3 months after treatment in 54.7%. No patient had neuroimaging evidence of tumor enlargement during the period of follow-up and 3 patients had imaging evidence of a slight decrease in tumor volume. Acute effects of SFR included headache, nausea, local erythema, and focal alopecia. None of these complications was severe or permanent, but radiation retinopathy was observed in 2 patients within 4 years of treatment. The retinopathy was severe in one patient and was associated with vitreous hemorrhage (45); the other patient had only retinal microaneurysms (41). This latter patient had a large tumor involving the proximal optic nerve adjacent to the globe, and portions of the retina received 54 Gy. Even so, visual acuity improved from 20/50 to 20/25 and remained stable. In a more recent report (49), radiation retinopathy occurred 22 months after SFR resulting in loss of visual acuity from 20/25 to 20/200. The posterior retina in this patient had received 50 Gy to 54 Gy. Other late ophthalmic complications of SFR included cataract in 1 patient, dry eye in 1, and iritis in 2 patients. None of the patients developed radiation optic neuropathy; however, 2 patients continued to lose vision from tumor progression. Late nonocular side effects included pituitary dysfunction in 3 patients and imaging evidence of punctate white matter lesions in the cerebral hemispheres in 1 patient. Both findings are a potential concern after irradiation for posteriorly located ONSMs, particularly those with mild but definite intracranial extension. Interval monitoring of pituitary function in such patients is thus appropriate.

**Surgery**

Extensive removal of ONSMs that extend for some distance within the optic nerve sheath or are located in the posterior orbit and/or optic canal is generally indicated only in rare cases in which there is aggressive tumor growth that extends intracranially and across the planum sphenoidale, thus presenting a risk to the contralateral optic nerve or disfiguring proptosis. Along with unavoidable and permanent blindness, such procedures may also cause temporary or permanent ophthalmoparesis, ptosis, or both. Unroofing the optic canal was previously advocated as a method of improving or at least maintaining visual sensory function in patients whose ONSMs were located entirely within the
TABLE 1. Summary of primary stereotactic radiotherapy series

<table>
<thead>
<tr>
<th>Authors (reference number)</th>
<th>Eyes</th>
<th>Period</th>
<th>Mean follow-up</th>
<th>Treatment modality</th>
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<tr>
<td>Liu et al (45)</td>
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<td>1994-2001</td>
<td>1–7 years</td>
<td>FSR</td>
<td>25–30 × 1.8</td>
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<td>1976–1999</td>
<td>12 months</td>
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<tr>
<td>Andrews et al (47)</td>
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<td>1996–2001</td>
<td>20.7 months</td>
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<td>28–30 × 1.8</td>
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<td>1999–2002</td>
<td>2 years</td>
<td>FSR</td>
<td>25–27 × 1.7–1.75</td>
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**Eyes** = The subset of eyes with measurable vision (counting fingers and better). **Treatment regimen** = The number of fractions × doses per fraction (Gy). **Stable, improved, worse** = The treatment effect on visual acuity and visual fields at the last follow-up, as defined by author. 3D-CFR = 3-dimensional conformal fractionated radiotherapy. CSFR = Highly conformal stereotactic radiotherapy. SFR = Stereotactic fractionated radiotherapy. *Transient complications not listed.

<table>
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<th>Authors (reference number)</th>
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<th>Complications*</th>
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<tr>
<td>Baumert et al (48)</td>
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<tr>
<td>Richards et al (35)</td>
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<td>5</td>
<td>0</td>
<td>0</td>
<td>Radiation retinopathy 4 years after treatment (vitreous hemorrhage) (1)</td>
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</table>

*Radiologically evident cerebral punctuate small vessel fall out in the field of irradiation (1)

**Complications**

- Hyperprolactinemia (2)
- Partial hypophyseal insufficiency (1)
- Dry eye (1)
- Iris (2)
- Cataract (1)
- Microaneurysms (1)
- Radiation retinopathy 4 years after treatment (vitreous hemorrhage) (1)

Eyelid opening (26); however, this treatment has been supplanted by radiation therapy (see previously) in large part because of the temporary nature of the improvement/stabilization with canal unroofing. On the other hand, as noted previously, in rare cases of anteriorly located, primarily exophytic tumors with focal involvement of the dural sheath, surgical excision is a potential treatment choice and can be performed without undue risk of iatrogenic visual loss (6), although most such cases are identified at surgery because it is extremely difficult to distinguish exophytic tumors from other lesions such as cavernous hemangiomas and solitary fibrous tumors that are simply adjacent to the optic nerve. Furthermore, optic nerve sheath decompression with release of trapped cerebrospinal fluid or removal of some tumor followed by radiation therapy may also be beneficial in some cases of acute visual loss (50), although as noted previously, when improvement does occur, it is likely to be transient unless stereotactic or conformal fractionated radiation therapy follows. A potential drawback of surgery is that it exposes the orbit to tumor extension.

**CONCLUSION**

The main goals in the management of ONSMs are ensuring a favorable visual outcome, establishing local control of the tumor, and minimizing the risks of treatment-related morbidity. Limitations for any treatment study of ONSMs include both the rarity and usually very slow course of the disease, the fact that there often is no tissue diagnosis so that some patients in a treatment trial could
have lesions other than an ONSM (sarcoidosis), the necessity of pooling data from multiple different treatment centers, and the need for a long (10 years) follow-up period to detect late recurrences and late side effects of the treatment.

In the 7 studies described here (6,35,41-45), the short-term efficacy of SFR in preserving or improving vision appears to be excellent with more than half of the patients having improvement within 3 months after treatment. The results also suggest that earlier treatment might offer a better chance of preserving useful vision. Based on the results of published studies, as well as my own experience, I believe that SFR is the best option for most cases of progressive or advanced disease. However, because of improved imaging, patients with presumed ONSMs associated with mild progressive or stable visual loss are being diagnosed earlier, and the choice between observation and radiation has become more difficult. I agree with others (51) that longer follow-up is needed to establish the incidence of enduring benefit and late toxicity after SFR and to clarify the optimal management of these cases.

REFERENCES


Pupil Abnormalities in Selected Autonomic Neuropathies

Fion D. Bremner, PhD and Stephen E. Smith, PhD

Abstract: Examination of the pupil provides an opportunity to detect disturbances in the autonomic innervation of the eye. The pupil is frequently affected in patients with generalized autonomic neuropathies. This literature review confirms a high prevalence of sympathetic deficits and parasympathetic deficits in acute or subacute dysautonomia, diabetes, amyloidosis, pure autonomic failure, paraneoplastic syndromes, Sjögren syndrome, familial dysautonomia, and dopamine β-hydroxylase deficiency. It confirms the relative scarcity of a pupil abnormality in patients with multiple system atrophy. There are difficulties in clinical diagnosis of pupil abnormalities and interpretation of pupil pharmacologic tests, particularly when combined sympathetic and parasympathetic deficits are present.


A utonomic neuropathy is characterized by cardiovascular, gastrointestinal, genitourinary, and sweat gland dysfunction. In most cases, sympathetic and parasympathetic branches of the autonomic nervous system are involved, although in a few instances, there is selective hypofunction in one or another branch. Pupil abnormalities have been widely reported in association with generalized autonomic failure but, except in diabetes, rarely investigated in detail.

In this review, we have used electronic (Medline, PubMed) and manual techniques to search the literature for published reports of pupil abnormalities in selected autonomic neuropathies. Most reports are anecdotal—based on clinical observations and only sometimes supported by confirmatory tests. With the exception of diabetes mellitus, there are no systematic studies of pupil involvement in these conditions. The findings have been grouped according to etiology, and we have assessed the evidence for the pupil signs before attempting to draw sweeping conclusions.

Because the pupil constrictor muscle is supplied by parasympathetic fibers and the dilator by sympathetic fibers, complete failure of iris innervation should result in a pupil of medium diameter that is unresponsive to light, near, and alarm stimuli, although persistence of adrenal medullary function might allow slow dilator responses to stress from circulating catecholamines. Very few such instances of "pupilloplegia" are reported except in cases of acute or subacute pandysautonomia.

Selective parasympathetic denervation should result in relative mydriasis in light and diminution in constrictor reflexes with or without pupillotonia (which is thought to result from aberrant reinnervation [1]). Selective sympathetic denervation should result in relative miosis in darkness with dilatation lag (2) and diminution of the startle reflex as seen in Horner syndrome (3,4). In all such instances, the pupil would be expected to show supersensitivity to topical administration of receptor agonists (2% or 2.5% methacholine and 0.1% or 0.125% pilocarpine at the sphincter muscle, 1% phenylephrine or 1% epinephrine at the dilator muscle).

ACUTE AND SUBACUTE DYSAUTONOMIA

This acute or subacute condition is characterized by widespread dysfunction of one, or more usually both, branches of the autonomic nervous system coupled occasionally with somatic sensory or sensorimotor impairment. In some cases, it follows an episode of influenza-like illness and recovery is variable.

Acute and subacute dysautonomia commonly involve the pupil. Published cases (Table 1) can be divided into several forms: a predominantly cholinergic type affecting the parasympathetic nervous system (5–19), an adrenergic type affecting the sympathetic nervous system (20,21), a mixed type (22–51,202), and forms with additional involvement of sensory (52–63) or sensorimotor peripheral nerves (64).

Despite differences in clinical presentations, the pupil findings in cases within the different groups are essentially
## TABLE 1. Pupil abnormalities in various forms of acute and subacute dysautonomia

<table>
<thead>
<tr>
<th>Predominant pattern of peripheral nerve involvement</th>
<th>Cholinergic (5–19)</th>
<th>Adrenergic (20–21)</th>
<th>Mixed (12,18,22–51,202)</th>
<th>Sensory and autonomic (18,52–63)</th>
<th>Sensorimotor and autonomic (64)</th>
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similar. The shape of the pupil is often oval or irregular in outline. Mydriatic pupils are described as having a poor reaction to a light stimulus or a target viewed at reading distance ("near target"). The only exception is one reported case of the acute adrenergic type whose pupils were small and who appeared to have bilateral Horner syndrome (20). The majority of patients have not undergone formal pharmacologic testing, but among patients who were tested, 75% showed evidence of sympathetic deficit (7,14,17,19,24-27,31,32,34,36,42,43,46,49,50,53,58-60) and 90% demonstrated parasympathetic deficit (7,8,10-12,14,17-19,22,25-28,31-37,40,42,43,46,53,58-60). Overall, the findings indicate that a high proportion of these cases involve both parasympathetic and sympathetic denervation of the pupil.

Recent observations suggest that these pupil abnormalities may result from widespread autonomic ganglionopathy and they are strongly linked to the presence of autoantibodies to ganglionic cholinergic receptors (65-67). Acute dysautonomia in cats and dogs also causes miosis, reduced or absent light reflexes, and supersensitivity to both pilocarpine and epinephrine (68-70).

**DIABETES MELLITUS**

The pupil is frequently abnormal in both types of diabetes mellitus: type 1 or insulin-dependent diabetes, which is commonly of early onset; and type 2 or noninsulin-dependent diabetes, which is usually of later onset.

The most common observation is that the pupil is miotic (71-77), particularly in darkness. A screening study of 359 unselected diabetic patients found that 21.7% had abnormally small pupils for age (78). Significant associations between small pupils and a wide range of diabetic complications have been recorded: cardiovascular autonomic dysfunction (79), peripheral sensory loss (73,77), retinopathy (80), nephropathy (73), and unchy prolonged and severe hyperglycemia (73,77). Acute hyperglycemia may cause miosis that reverses when normoglycemia is established (81,82).

The common occurrence of a small pupil with intact light reflexes, in contrast to the rarity of a large pupil with poor light reflexes, suggests that the sympathetic iris innervation is more susceptible to damage than the parasympathetic innervation. Histologic studies of irides removed from patients with diabetes during cataract surgery have confirmed that loss of nerve terminals occurs preferentially from the dilator pupillae (83,84). The reason for the greater susceptibility of the sympathetic nerves is unknown; it may be related to the greater length of the nerve pathway (90).

The mydriatic response to direct-acting sympathomimetic agents is exaggerated in patients with diabetic autonomic neuropathy (79,80), implying denervation supersensitivity (85,86). In one study (79), severe miosis was found to be associated with supersensitivity to phenylephrine but normal responses to the indirect-acting sympathomimetic hydroxyamphetamine. These findings indicate that diabetic miosis is at least partly neuropathic in origin but that the postganglionic neuron remains functionally intact. It seems unlikely that diabetes blocks transmission of sympathetic impulses at any one point along the sympathetic pathway; more probably the deficit results from a composite of mildly reduced function throughout.

The anticholinergic drug tropicamide produces less mydriasis in diabetic pupils than in nondiabetic pupils, presumably because of the loss of effective pupil dilator function. Some observers have used measurement of the pupil response to a large dose of an anticholinergic to assess dilator muscle function and thus, indirectly, the percent of diabetic neuropathy (75,87). Full mydriasis in practice requires combined instillation of tropicamide and phenylephrine (88).

The amplitude of the pupillary constriction to light is reduced in diabetic pupils (89,90). Light reflexes, if present, are slow in onset and time course, giving prolonged latency times and reduced maximum velocities of constriction and redilatation (77). This reduction is usually found only in pupils that are already small from sympathetic dysfunction. In severely affected patients, therefore, pupil size remains almost constant despite wide changes in illumination. There are a number of possible explanations for this. First, neovascularization of the iris (rubecsis) may have stiffened the iris and immobilized the pupil. Recent evidence also shows that patients with type 2 diabetes can develop iris transillumination defects, particularly if there is severe retinopathy, suggesting hypoxic damage to the iris (91). Second, retinopathy and laser photocoagulation treatment attenuate the afferent limb of the pupil light reflex. Third, it is likely that damage to the parasympathetic supply underlies at least some of the observed reduction in pupil light responses. The pupil will constrict after topical administration of pilocarpine (80), and light reflexes are attenuated even after adjustments are made to the stimulus intensity to take into account differences in retinal sensitivity (90). Presumably, the iris in such patients is essentially denervated in both autonomic branches. The enhanced response of the diabetic pupil to cholinomimetic agents such as pilocarpine (80) supports this hypothesis.

Random variation in the pupil diameter when the eye is exposed to constant illumination, known as hippus, is always symmetric in the two eyes and thought to be central in origin (92). Patients with diabetes with neuropathy show reduced hippus compared with healthy subjects (77,93). It is not clear whether this phenomenon is the result of peripheral damage to the autonomic nerves and iris muscles or whether the central control centers for pupil size are affected.
AMYLOIDOSIS

Systemic amyloidosis consists of a heterogeneous group of conditions characterized histologically by deposition of abnormal birefringent protein in tissues. The protein responsible for most cases of familial amyloid (AF) polyneuropathy is transthyretin, whereas the most common form of acquired amyloidosis (AL) involves deposition of light-chain paraproteins.

Clinical features suggestive of widespread damage to the autonomic nervous system are well recognized, although uncommon, in both AF and AL. In their survey of 229 cases of AL seen at the Mayo Clinic, Kyle and Greipp (94) reported 31 (14%) patients who had orthostatic hypotension. Among the subset of patients with AL who develop polyneuropathy, however, autonomic dysfunction appears to be common. Thus, Trotter et al (95) found orthostatic hypotension in 8, bowel upset in 9, and impotence in 8 of 10 patients. There is histopathologic evidence of amyloid deposition in the sympathetic ganglia and sympathetic chain (96-99).

The most apparent ophthalmic manifestation of amyloidosis is amyloid deposition in the lids, extraocular muscles, ocular adnexae (100-104), and the eye, especially the vitreous gel (105-108). Pupillary abnormalities have been reported, usually in association with other evidence of autonomic dysfunction. In 21 reported cases (Table 2), the pupil abnormality was reported as hyporeactive (109), asymmetric or unreactive (95), or showing light-near dissociation (110-112). One case (112) was reported as having bilateral “Holmes-Adie” pupils, parasympathetic denervation being confirmed by finding supersensitivity to methacholine (96). These pupil abnormalities are consistent with a parasympathetic deficit for which amyloid deposition in the ciliary ganglion may be responsible (113,114). Bilateral pupil dilatation lag, which indicates a sympathetic deficit, has also been reported in patients with amyloidosis and autonomic neuropathy. In at least one of these cases, amyloid deposition in the sympathetic chain appeared to be responsible (115).

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA; Shy-Drager syndrome) is a progressive condition associated with a variable incidence of extrapyramidal disorder with parkinsonism, cerebellar dysfunction, and dysautonomia. The condition is often accompanied by a sleep disturbance and bladder dysfunction. It is notoriously unresponsive to antiparkinsonian medication.

Pupil abnormalities are occasionally found in MSA (Table 2). In their original description of this condition, Shy and Drager (116) described iris atrophy and anisocoria in both of their patients. One of them had ptosis and miosis in one eye and also had reduced pupillary reactions to light and near. Anisocoria has appeared frequently in subsequent reports (117-123), although some patients with MSA may have had unilateral Horner syndrome (117,118,124) or alternating Horner syndrome as reported in 6 patients (125-127). The mechanism is obscure.

Despite widespread autonomic dysfunction, however, many patients with MSA have been found to have normal pupils. In one series (117), 40 (70%) of 57 patients had normal pupils, and the pupils have been reported as normal in this condition by many others (42,124,126,128-130).

PURE AUTONOMIC FAILURE

Pure autonomic failure (PAF) is a variably progressive idiopathic condition often occurring in later life in which there is widespread autonomic dysfunction without disturbance of the central nervous system or involvement of the peripheral somatic nerves.

The pupil has been rarely studied in detail in PAF. In their original study, Bradbury and Eggleston (131) observed that the pupils of their two patients were misshapen but that they reacted normally. Although many patients have no pupillary abnormality (24,132-135), absent light reflexes with light-near dissociation have been reported once (136). Bilateral ptosis has been observed (24) and Horner syndrome reported (4,133,135) with adrenergic supersensitivity found in 3 cases. Polinsky et al (133) reported that tyramine, an indirect-acting sympathomimetic agent similar to hydroxyamphetamine, was associated with reduced pupillary dilatation in patients with PAF relative to controls. This difference is consistent with the belief that PAF is a disease of peripheral neurons, whereas MSA is a disease of central neurons.

PARANEOPLASTIC SYNDROMES

Immune responses to tumors may cause remote (nonmetastatic) effects on specific target organs, including peripheral nerves, giving rise to various paraneoplastic syndromes.

Pupil abnormalities have been widely reported in patients with a number of paraneoplastic syndromes, including Lambert-Eaton myasthenic syndrome (LEMS) (Table 2). Bilateral tonic pupils, absent or sluggish reactions to light, and prolonged pupil cycle times have been described in 13 LEMS cases (137-143). Unspecified pupil dysfunction has been noted in 4 cases (144), and supersensitivity to cholinergic (139,141,145-148) and adrenergic (141,149) agents in 8 cases. The aggregate frequency of reported pupil abnormalities in LEMS is 24% (21 of 88) (150).

Pupil abnormalities also occur in other paraneoplastic syndromes. Bilateral tonic pupils with pilocarpine...
### TABLE 2. Pupil abnormalities in acquired amyloidosis (AL), multiple system atrophy (MSA), pure autonomic failure (PAF), and Lambert-Eaton myasthenic syndrome (LEMS)

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<th>AL Amyloid (95–96,109–115)</th>
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<th>PAF (4,24,131–136)</th>
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supersensitivity have been reported in 3 infants with neuroblastoma (147,148) and in adults with presumed anti-Hu-mediated neuropathies associated with small cell lung carcinoma (151–154), adenocarcinoma of the colon (155), and testicular seminoma (145). There is one report of bilateral Horner syndrome associated with anti-Hu-mediated demyelinating neuropathy and small cell lung carcinoma (156). Unilateral tonic pupils with or without cholinergic supersensitivity have been reported in 4 cases (157–160), but the pupillotonia may be indicative of coincidental Holmes-Adie syndrome (3 of the 4 cases had tendon areflexia) and are therefore difficult to interpret.

SJÖGREN SYNDROME

SJö gren syndrome is characterized by keratoconjunctivitis sicca, xerostomia, and numerous extraglandular manifestations that may overlap with rheumatoid arthritis. When these manifestations are part of another connective tissue disorder, SJö gren syndrome is considered secondary.

Autonomic neuropathy is a common complication of primary and secondary SJö gren syndromes. Unilateral or bilateral tonic pupils occur, usually with light-near dissociation (161–172). Similar findings have been reported in patients with sicca syndrome in whom a definitive diagnosis of SJö gren syndrome had not yet been made (173,174). The recent demonstration of autoantibodies against M3-muscarinic acetylcholine receptors in patients with SJö gren syndrome suggests that the pupil abnormality may be caused by receptor blockade rather than sphincter muscle denervation in some cases (175,176).

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY TYPE III (RILEY DAY SYNDROME, FAMILIAL DYSAUTONOMIA)

The familial condition of hereditary sensory and autonomic neuropathy type III (HSAN III), occurring almost exclusively in Ashkenazi Jews, is characterized by widespread sensory and autonomic disturbance. The hallmark ophthalmic signs of HSAN III are alacrima and corneal hypesthesia (177); ulceration and scarring of the corneas are common and blindness may occur.

Pupil abnormalities have been widely reported in HSAN III, largely on the basis of pharmacologic evidence. The most common feature, an exaggerated miotic response to 2.5% topical methacholine or 0.1% or 0.125% pilocarpine, is usually attributed to denervation supersensitivity of the iris sphincter muscle (178–189). Such supersensitivity is no longer regarded as pathognomonic of the condition because it is to be expected in any other condition in which there is parasympathetic denervation (190). Moreover, not all the evidence supports parasympathetic dysfunction. Three early studies (188,191,192) showed that the pupils of these patients react normally to light and a near target, and that there is no pupillotonia or light-near dissociation. The responses to topical anticholinesterases (physostigmine, neostigmine, and echothiophate) have also been unremarkable in some patients with HSAN III (or in a single case, slightly exaggerated [178]). Such findings would suggest that the parasympathetic innervation in HSAN III is intact.

In most patients with HSAN III, the autonomic neuropathy is characterized principally by sympathetic deficits with parasympathetic dysfunction sometimes occurring. Pupil sympathetic function has rarely been studied in detail. Normal responses to both cocaine and epinephrine were reported in 20 patients (178,181) and an exaggerated response to phenylephrine in only one (180). A recent study comparing pupil measurements in 14 patients with age-matched healthy controls showed a reduction in pupil diameter in darkness and redilatation velocity, as well as attenuation of the light reflex, possibly indicating mixed sympathetic and parasympathetic failure (193). The differences found were surprisingly small but did achieve statistical significance.

DOPAMINE β-HYDROXYLASE DEFICIENCY

In dopamine β-hydroxylase deficiency, a rare inherited condition, subjects lack the enzyme dopamine β-hydroxylase and therefore cannot synthesize norepinephrine from dopamine, causing a pure sympathetic deficit (194–199).

The pupils have been described as small (2–3 mm in diameter) but normally reactive (194,195,197) with supersensitivity to topical epinephrine (198) and phenylephrine (197) but no response to hydroxyamphetamine (196), the indirect action of which requires a functional postganglionic sympathetic neuron. Later pupillographic studies of a sibling pair (198) revealed severe bilateral redilatation lag (4) consistent with these abnormalities. As expected, the pupils showed no supersensitivity to methacholine (194,196,198) and did not dilate with the atropinic agent homatropine (196).

GENERAL COMMENTS

A systematic literature review confirms that patients with widespread autonomic dysfunction are often reported as having abnormal pupils. For several reasons, the detection and characterization of these pupil abnormalities can be challenging. The initial clinical examination is often unremarkable because the pupil abnormalities are commonly bilateral and symmetric. The pupils are rarely misshapen even when tonic; anisocoria may not be present under any lighting conditions; and clinical detection of an abnormal response to light or near has a low sensitivity.
Reports of abnormal pupils associated with generalized dysautonomia are therefore likely to underestimate their actual prevalence if based on clinical observations alone. It should be possible to overcome these difficulties in part by using pharmacologic tests to demonstrate denervation supersensitivity to weak receptor agonists. However, care must be taken in the interpretation of such findings because many patients with autonomic neuropathy have impaired tear formation with or without corneal damage. In such circumstances, transcorneal drug penetration may be enhanced (188), thus giving rise to an apparent but false supersensitivity (200). This is well illustrated by a recent report of a patient with Sjögren syndrome with dry eyes in whom both pupils were supersensitive to norepinephrine but there was no impairment of the sympathetic supply as demonstrated by a normal mydriatic response to cocaine (201). Drug testing may therefore tend to overestimate the prevalence of pupil abnormalities in patients with tear film disturbance. Furthermore, the lack of a "control" eye and the possibility that both parasympathetic and sympathetic supplies are affected make interpretation of pupillary responses to different drugs particularly difficult.

In many patients with dysautonomia, iris sphincter and dilator muscles are both likely to be denervated to some percent, but if one deficit predominates, it will mask the other. For example, a patient with bilateral tonic pupils may also have a sympathetic deficit. However, with isoscopy and symmetric lids, and without a "control" eye against which to compare redilatation times or responses to topical cocaine, it is impossible to prove any sympathetic deficit. A patient with bilateral Horner syndrome might also have a mild parasympathetic deficit, but the subtle changes in light diameter and responses to light and a near target would be masked by the changes in resting diameter resulting from the sympathetic deficit. Drug tests may be useful but the results should be interpreted with caution. In practice, pupil abnormalities are most commonly interpreted as indicating either sympathetic or parasympathetic denervation; it is rarely possible to diagnose confidently damage to both arms of the autonomic system in the pupils of an individual patient.

REFERENCES

The Pupil in Autonomic Neuropathies


The Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida
April 30–May 4, 2006

Some 5,920 abstracts were presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), Fort Lauderdale, Florida, April 30–May 4, 2006. Available on www.arvo.org, the abstracts are referenced by program number.

In their keynote address, Paul Sieving, MD, PhD, Director of the National Eye Institute and G.N. Rao, MD, President, International Agency for the Prevention of Blindness (IAPB), emphasized the importance of building global partnerships in performing vision research as a vital method for the control of avoidable worldwide blindness. Among this year’s presentations, well over half were multi-country collaborations. The Proctor Medal winners were Trevor D. Lamb, BE, ScD, FRS (Cambridge, U.K.) and Edward N. Pugh, Jr., PhD (Philadelphia, PA), who, in an elegant joint presentation, discussed their work on “The Vision Cycle.” The Weisenfeld, Friedenwald, and Cogan awards were given to S. Evangelos Gragoudas, MD (Boston, MA), David Williams, PhD (Rochester, NY), and Joshua L. Dunaief, MD, PhD (Philadelphia, PA) for their contributions to the field of uveal melanomas, human vision, and pathogenesis of age-related macular degeneration, respectively.

NEUROPROTECTION AND OPTIC NERVE PHYSIOLOGY

When investigating the cellular and molecular mechanisms underlying optic nerve degeneration after axotomy, it was concluded that cell invasion (microglia, oligodendrocytes, astrocytes), semaphorin induction, the presence of myelin debris, and disruption of the internal organization of the optic nerve contribute to the generation of the nonpermissive environment that prevents axonal regeneration and leads to neuronal loss (#727). Optic nerve crush induced a slower rate of retinal ganglion cell (RGC) progressive degeneration than did optic nerve transection (#1248). Nicotinamide adenine dinucleotide may be neuroprotective for tumor necrosis factor alpha-induced small fiber optic nerve axonal death and may hold potential for the treatment of some optic neuropathies (#730). Transpupillary thermotherapy led to greater survival of RGCs at 2 weeks in comparison to the control group after optic nerve crush produced at a distance of 1 mm from the disc by an aneurysm clip for 60 seconds (#1571). Treatment with minocycline was found to inhibit neuroglial cell activation and increase neuronal survival, inhibit caspase-dependent and caspase-independent pathways of neuronal death, and increase survival of retinal neurons up to two weeks after ischemic injury to the optic nerve (#1572). Therapeutic doses of insulin-like growth factor, a central nervous system neuroprotective agent, can reach the retina and optic nerve of rats by intranasal delivery (#728).

OPTIC NEUROPATHY

Two studies suggest a possible link between coagulation abnormalities and ischemic optic neuropathy. In the first study, 5 patients with optic neuropathy and elevated alpha-2 antiplasmin levels were reported. Patients’ ages ranged from 45 to 76 years. Acuity ranged from 20/20 to counting fingers. All patients showed gradual improvement on repeat visual field administration, but no defects completely resolved. All patients had painless vision loss with either optic disc pallor or segmental nerve fiber layer hemorrhages (#731). In the second study, 8 patients with optic neuropathy and alpha-1 antitrypsin deficiency were identified. Alpha-1 antitrypsin is a major circulatory serine protease inhibitor involved in the coagulation cascade, including the protein C pathway. Visual acuity ranged from 20/25 to hand motions. All patients presented with varying degrees of bilateral optic pallor and were found to have low alpha-1 fraction (alpha-1 globulin) on protein electrophoresis ranging from 0.04 g/dL to 0.15 g/dL (normal, 0.14–0.26 g/dL). No patients were noted to have lung disease or clotting abnormalities. All patients had normal neuroimaging studies (#732). The mechanism for indirect traumatic optic neuropathy is not well established. Previous work has postulated that force is conducted through the sphenoid bone to the optic canal and induces structural deformation of the surrounding bone. The authors propose that optic nerve injury is at least in part the result of soft tissue (rather than bone) energy transmission, which is amplified within the conical space of the orbit. An impact hammer was designed to deliver a blunt force to a human cadaver head. Accelerometers were placed within the orbit.
and on the superior scalp. Movement was recorded after impact directed to the forehead and back of the skull. Frontal impact resulted in high-frequency oscillations, which were not seen with posterior impacts, consistent with a reverberation effect within the orbit (#741).

**ISCHEMATIC OPTIC NEUROPATHY**

In a rat model of ischemic optic neuropathy, optic nerve segments were cultured in vitro in oxygen and glucose-deprived conditions for 2 hours. Connexin 43 gap junction specific antisense oligodeoxynucleotides were shown to reduce cell death and tissue swelling in the cultures. The degree of upregulation of connexin 43 was directly correlated with the severity of tissue damage (#740). In a different rat model of ischemic optic neuropathy, bone marrow-derived stem cells were injected intravenously or intravitreally after induction of optic nerve ischemia. Stem cells were injected one day before, immediately, or one day after ischemia induction. Stem cells were incorporated at both retinal and optic nerve injury sites within 3 days of injury and survived for at least 30 days (#772). In 3 patients with nonarteritic ischemic optic neuropathy and 2 patients with traumatic optic neuropathy, transcorneal electrical stimulation for 30 minutes led to the appearance of isopters to dimmer light stimulus intensities 1 to 3 months after treatment (#733).

**OPTICAL COHERENCE TOMOGRAPHY**

The effect of optic nerve compression on amplitude and phase of pattern electroretinogram (ERG) and retinal nerve fiber layer (RNFL) thickness was studied in 36 patients with compressive optic neuropathies. The patients were tested with pattern ERG (PERG), visual-evoked potentials (VEPs), perimetry, and optical coherence tomography (OCT) to measure RNFL thickness and were compared with 20 normal subjects. The study concluded that compression of the intraorbital part of the optic nerve can cause abnormalities in amplitude and/or phase of the PERG even before axonal loss occurs. Abnormalities in PERG latency may consist of prolongation or shortening of the conduction time. Factors that influence whether the latency time is longer or shorter may relate to which population of ganglion cell axons are affected by compression in a given person. PERG amplitude but not latency appears to correlate with RNFL thickness (#663).

The RNFL and macular thickness were studied in 40 patients with band atrophy of the optic nerves and temporal hemianopic visual field defects resulting from chiasmal compression. Macular and RNFL thickness were assessed with a Stratus OCT. The severity of visual field defects was evaluated by the mean defect from automated perimetry. Macular thickness parameters related to the nasal hemiretina could best detect pathologic damage in eyes with band atrophy. Macular thickness measurements in eyes with band atrophy were significantly lower than those in healthy eyes. Macular thickness measurements represent a surrogate indicator of ganglion cell loss in patients with band atrophy and could prove to have clinical value for detection of damage and for long-term monitoring (#748).

**PERIMETRY**

RNFL measured by OCT and visual field sensitivity were correlated in 30 eyes with compressive optic neuropathy. The study demonstrated that the papillomacular bundle was most frequently affected (73%) and had the most significant loss (54%) of RNFL thickness. The authors demonstrated that RNFL thinning topographically correlated with decreased visual field sensitivity in compressive optic neuropathy and that this structure–function relationship suggested that RNFL thickness as assessed by OCT predominantly measures irreversible axonal loss (#1084).

**LEBER HEREDITARY OPTIC NEUROPATHY**

Two studies showed that the optic disc in unaffected carriers of Leber hereditary optic neuropathy (LHON) is larger than the mean size in the general population and that the clinical expression of LHON may be influenced by the size of the optic disc (#753). A smaller vertical optic disc diameter as determined by OCT was correlated with a lack of recovery of vision in patients with LHON (#756).

A fundamental paradox of LHON is that although all cells in the body have the same mtDNA mutations, the disease is almost exclusively manifested in RGCs. RGCs use superoxide as a mitochondrial-derived intracellular messenger for signaling the initiation of apoptosis after neuronal injury. Some investigators have speculated that differences in reactive oxygen species production and sensitivity to oxidative stress among cell types may explain the timing and specificity of LHON. The authors examined superoxide production in isolated RGC mitochondria using a novel RGC cell line and brain from rats. The rate of superoxide production was 7 times lower in the cell line than in brain mitochondria corrected for protein. There was a dramatic difference in superoxide production when electrons were shunted to complex I using mitochondrial electron transport chain complex I and III substrates and inhibitors. Mitochondrial DNA mutations of specific components of NADH-ubiquinone oxidoreductase in LHON may disrupt the cell type-specific handling of superoxide in RGC mitochondria and lead to premature cell death (#2571).

**OPTIC DISC DRUSEN**

There are two possible explanations for blind spot enlargement associated with optic disc drusen: physical
enlargement of the optic disc by drusen and peripapillary serous retinal elevation. Quantitative analysis in one study suggested that physical enlargement of the optic disc by drusen is the cause. This study revealed a statistically significant greater disc area as detected by OCT. Average optic disc area measured by OCT was 65% greater than normal. This difference is not explained by refractive error, axial length, or corneal curvature (#744).

OCT can detect RNFL defects in patients with optic disc drusen. OCT detected a defect in more hemifields (65%) than did automated perimetry (54%) or multifocal VEP (38%). Although OCT tended to be abnormal when both automated perimetry and multifocal VEP were abnormal (94%), it was abnormal 48% of the time when both perimetry and visual-evoked potentials were normal and 51% of the time when one or both of these tests were normal. Given the low false-positive rate (1.7%), OCT may be useful in detecting RNFL damage in patients with optic disc drusen (#754).

In a prospective study, 31 (39%) of 80 eyes with optic disc drusen showed visual field deterioration after a mean follow-up time of 77 months. The older the patients with disc drusen, the higher the degree of visual field loss and the higher the amount of progression of visual field loss (#764).

**ORBIT AND OCULAR ADNEXAE**

In patients with large periorcular skin defects, the use of acellular human dermal matrix (AlloDerm) was shown to be very useful in situations in which autologous skin grafting may be extremely difficult (#3774). In patients with traumatic medial canthus tendon avulsion involving the inferior canaliculus, a new technique of repair was illustrated that emphasized reapproximation of the posterior crus of the medial canthal tendon (#3773). High-resolution MRI of the upper eyelid with surface coils was found to be useful in the preoperative identification of the upper eyelid skin crease, position of the septum, levator, and the orbital fat pads that resulted in better preoperative planning of ptosis surgery (#3777). Precision studies were conducted in an experimental orbit model to localize the electromagnetically tracked orbital endoscope for use with the free electron laser. Accuracy studies in the phantom trials revealed that the error was consistently between 2 and 3 mm, suggesting the need for further development (#3784). A study of surgical orbital decompression in 12 pediatric patients with Graves ophthalmopathy found that children have a relatively benign course and a lower surgical risk and morbidity than adults (#3785).

**EXTRAOCULAR MUSCLES AND EYE MOVEMENTS**

The polymerase chain reaction test substitutes for a muscle biopsy or lumbar puncture in confirming the diagnosis of a common deletion at 4977 bp in Kearns-Sayre syndrome (#4619). Surprisingly, the extraocular muscles (EOMs) seem to be spared in Duchenne muscular dystrophy that results in widespread muscle damage. An experimental study using C57BL/10 mice found that there were 15 times more stem cells per gram of tissue in extraocular muscles than in tibialis anterior. This greater stem cell density may be responsible for EOM-sparing and has the potential of leading to treatment strategies (#5059). In another experimental study, EOM mitochondrial ultrastructure and function was compared in hyperthyroid C57BL/6 mice and another hyperthyroid transgenic strain (adenosine nucleotide translocator 1-deficient [ANT1-/-], a mitochondrial-deficient model). Electron and confocal microscopy demonstrated a significant alteration in the number and function of mitochondria in the ANT1-/- mice, demonstrating that mitochondria are probably the site of derangement in thyroid-related eye disease and allowing determination of future therapeutic strategies (#5401). A session was devoted to the functional anatomy, computational and primate modeling, and central neural adaptations of superior oblique palsy (#449). In an experimental study using force generation as an end point in the rabbit superior rectus muscles that received a combination of injection botulinum toxin and ricin-m-Ab35, the authors concluded that this combination may be beneficial in extending the duration of the drug effect to weaken the EOM (#5395).

**PUPIL**

A clinical study involving 73 patients with isolated third cranial nerve palsy caused by microvascular ischemia (group 1) and 45 patients with a palsy caused by unruptured posterior communicating artery aneurysm (group 2) showed that the only clinical features that distinguished the two groups were a complete palsy of the somatic portion of the nerve (EOMs and lid) and normal pupil function (ischemia) (#781).

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The 58th Annual Meeting of the American Academy of Neurology
San Diego, California
April 1–8, 2006

The 58th Annual Meeting of the American Academy of Neurology (AAN) was held in San Diego, California, April 1–8, 2006. There were 1,580 scientific abstracts presented and a very full educational program.

Neuro-ophthalmology and neuro-otology courses and scientific presentations were very well attended this year in part as a result of a recent innovation at the AAN: the enhanced vertical integration (EVI) program. This program comprises a day that integrates many aspects of select subspecialties, allowing an AAN attendee the ability to concentrate on that subspecialty for the entire day. In addition to a cluster of courses, the day included a private poster session and a scientific session followed by a more in-depth session and panel discussion.

The scientific portion of EVI began with a neuro-otology poster blitz with discussion of the posters by Michael Halmagyi, MD (Sydney, Australia), David Zee, MD (Baltimore, MD), and John Leigh, MD (Cleveland, OH). The scientific platform session, chaired by Kathleen Digre, MD (Salt Lake City, UT) and Mark Moster, MD (Philadelphia, PA), consisted of a presentation of 6 abstracts focused mainly on mitochondrial disorders. This was followed by a session devoted to the mechanisms of optic nerve injury and neuronal death and featured Valerio Carelli, MD (Bologna, Italy) speaking on hereditary optic neuropathies, Leonard Levin, MD (Montreal, Quebec, Canada) speaking on mechanisms of axonal injury, and Robert Weinreb, MD (San Diego, CA) speaking on mechanisms of cell injury in glaucoma. Nancy Newman, MD (Atlanta, GA) chaired the session.

Elizabeth Engle, MD (Boston, MA) delivered the Sydney Carter Award Lecture at the presidential plenary session on the subject of ocular motility disorders arising from errors in brainstem motor neuron development. She discussed a classification of these entities as congenital cranial dysinnervation disorders (CCDDs). She described the conditions that primarily affect horizontally acting extraocular muscles, including Duane syndrome, horizontal gaze palsy with progressive scoliosis, and Möbius syndrome.

Of the many scientific abstracts presented, the following had particular interest to neuro-ophthalmologists.

OPTIC NEURITIS AND MULTIPLE SCLEROSIS

Three studies of optical coherence tomography (OCT) in optic neuritis and multiple sclerosis (MS) were reported.

A measurement of macular volume and retinal nerve fiber layer (RNFL) thickness with OCT-3 was performed in patients with MS (n = 70 [140 eyes]) and in disease-free controls (n = 29 [58 eyes]). Visual function was tested with low-contrast letter acuity (Sloan charts, 1.25%) and Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity. Total macular volume and RNFL thickness were lower in MS compared with controls (6.48 mm$^3$ vs 6.86 mm$^3$ for macular volume, 88 |Jim vs 98 |Jim for RNFL thickness; $P < 0.0005$) and were reduced even in eyes with no history of optic neuritis (ON). Lower vision scores were associated with reduced macular volumes and RNFL thickness. Measurements of macular volume and RNFL thickness were able to distinguish patients from controls and separate MS eyes with and without an ON history. However, direct correlations of overall RNFL thickness and total macular volume were only within the moderate range ($r_s = 0.60$, $P < 0.0001$), suggesting to the authors that these two parameters may capture different aspects of the disease (Osborne B, Philadelphia, PA, EV5.006).

A study of RNFL thickness using OCT-3 compared 60 patients with a single episode of ON (nonrecurrent ON), 10 patients with recurrent ON, and 27 patients with relapsing–remitting MS (RRMS). Those with recurrent ON had the thinnest RNFL (66 |Jim), those with RRMS 93 |Jim, and those with nonrecurrent ON 81 microns in the affected eye and 100 |Jim in the unaffected eye. Decreased RNFL measurements correlated with poorer visual acuity and worse visual fields (Costello F, Ottawa, Ontario, Canada, EV4.013).
Another prospective study found a reduced RNFL thickness, as measured by OCT, in patients with MS with or without a history of ON. This small prospective study evaluated 61 patients with MS and 20 controls every 6 months over an 18-month period. RNFL thickness and the presence of retinal periphlebitis were associated with disease activity in MS as measured by T2 and enhanced T1 MRI. Six (9.8%) of 61 patients developed retinal periphlebitis, which was associated with clinical relapses (P < 0.05). These findings suggest that RNFL thickness and the presence of retinal periphlebitis could be used as substitute markers of disease activity in MS (Villoslada P, Pamplona, Spain, S22.003).

A study looked at mitochondrial function in animals with experimental allergic encephalomyelitis, an animal model used to study MS. Oxidative injury to the mitochondrion began 3 days after antigen sensitization, even before any inflammatory cell infiltration. Reductions in adenosine triphosphate (ATP) synthesis of 94% in retinal ganglion cells were even greater than those associated with mitochondrial diseases. Mice that received intravitreal recombinant AAV-SOD2 to suppress oxidative injury had a rescue of ATP synthesis by 55%, a suppression of myelin fiber injury by 51%, and a fourfold increase in retinal ganglion cell survival 1 year later. This study implicates a mitochondrial process in the axonal and neuronal loss in MS (Qi X, Gainesville, FL, EV5.005).

A study of 117 brain biopsies in patients with pathologically proven MS and sufficient cortical tissue for analysis were reviewed for evidence of cortical demyelination. The biopsies were performed for diagnostic purposes within days to weeks of clinical presentation. Cortical demyelination was present in 21% of biopsies. Perivascular T-lymphocyte density was similar in cortical and white matter plaques, but paracortical T cell density was less. Microglia predominated in all cortical plaques. Early active cortical demyelination characterized by myelin degradation products within macrophages was present in a subset of cases. MS cortical plaques were present in the subpial cortex, within the cortex, and in subcortical white matter. The lesions showed dramatic evidence of inflammation and tissue destruction. These findings contrast with prior reports emphasizing the noninflammatory nature of cortical plaques, but the prior reports may be biased toward patients with longstanding disease (Roemer S, Gottingen, Germany, P02.080).

An MRI study of newly enhancing lesions was performed as part of the BECOME study, which compares interferon beta-1b (IFNB-1b; Betaseron) with glatiramer acetate (Copaxone) for RRMS and clinically isolated syndromes (CIS). In that study, 406 newly enhancing lesions were identified with a mean of 0.6 per patient per month using a 3-Tesla MRI and triple-dose gadolinium. In 62% of lesions, the enhancement lasted less than 1 month, in 34% for 1 to 3 months, and in 4% for longer than 3 months. Twenty lesions were hypointense on T1 MRI at 3 months. Nineteen of these 20 lesions fulfilled criteria for black holes at 6 months. Larger lesions were more likely to show prolonged enhancement and to progress to black holes (Gomez-Choco MJ, Canary Islands, Spain, P02.093).

Eleven patients with diplopia as part of a CIS were reported. Seven patients had sixth cranial nerve palsy, 3 had internuclear ophthalmoplegia, and 1 had partial third cranial nerve palsy. All had MRI lesions consistent with demyelination and negative diffusion-weighted studies but 4 had initially negative reports by the radiologist. All 9 patients followed up for at least 6 months had significant improvement. Three have progressed to clinically definite MS (CDMS) (Pula J, Peoria, IL, P01.027).

Prior studies of antimyelin antibodies as a predictor for developing CDMS have had conflicting results. In a study reported here of 51 patients with CIS, 28 (54.9%) had either double or single positivity for antimyelin (anti-MOG or anti-MBP) antibodies. Antibody status significantly predicted development of MS based on Poser (but not McDonald) criteria (P = 0.004) with a higher proportion of patients converting to MS in the antibody-positive group (P = 0.027). However, patients who were anti-MBP-positive developed a significantly higher number of T2-hyperintense lesions than did patients who were anti-MBP-negative (anti-MBP+ 9.28 ± 10.45 vs anti-MBP- 3.96 ± 5.12, P = 0.03) (Tomassini V, Rome, Italy, P02.107).

The BENEFIT trial reported the results of 250 μg IFN1b administered subcutaneously every other day in patients with a clinical demyelinating event and 2 clinically silent MRI lesions. Primary efficacy end points were time to CDMS and time to diagnosis of MS according to the McDonald criteria. IFN1b significantly delayed the progression from the first clinical event to CDMS (log-rank test P < 0.0001) and McDonald criteria-defined MS (P < 0.00001). According to proportional hazards regression analysis adjusted for standard baseline covariates, the risk of CDMS in the IFNB-1b group was reduced by 50% (hazard ratio with 95% confidence interval [CI]: 0.50; 0.36–0.70) and for McDonald criteria-defined MS by 46% (0.54; 0.43–0.67), respectively. The Kaplan-Meier estimates of the percentage of patients who fulfilled the criteria for CDMS within 24 months were 45% in the placebo group and 28% in the IFNB-1b group. IFN1b prolonged the time to CDMS by 363 days based on the 25th percentiles. The BENEFIT study demonstrates that IFN1b administered according to that regimen significantly delays progression to definite MS in patients with a first clinical demyelinating event suggestive of MS (Freedman M, Ottawa, Ontario, Canada, S02.001).

Twenty patients with RRMS with acute exacerbations were included in a study of intravenous immunoglobulin...
natahzumab is the development of progressive multifocal leukoencephalopathy (PML). Ten patients received 0.4 g/kg IV Ig per day for 5 days and ten patients received 1,000 mg IVMP per day for 3 days. In both groups, the Expanded Disability Status Scale score improved significantly after the treatment of relapse with no difference seen between the two groups. Brain MRI showed significant reduction of T2, FLAIR, and enhanced T1 lesion volumes in the IV Ig group, whereas no such finding was observed in the IVMP group. The authors conclude that IV Ig is effective and well tolerated in the treatment of acute MS relapses. However, there was no untreated control group in this study (Kuosisto H, Tampere, Finland, P01.069).

New sensitive measures of visual function in MS have been evaluated over the past year. Low-contrast letter acuity was used in 2 clinical trials of natalizumab to measure the drug's potential to preserve visual function in patients with MS. The AFFIRM (natalizumab vs placebo) and SENTINEL (natalizumab plus interferon beta 1a vs placebo plus interferon beta 1a) were multicenter, randomized, double-blind trials in patients with RRMS. Although high-contrast letter acuity was not able to show a treatment effect after 24 months, low-contrast letter acuity testing (1.25% and 2.5% Sloan charts) showed sustained reductions in vision loss in the AFFIRM (hazard ratio: 0.73, CI: 0.58-0.91, \( P = 0.006 \)) and SENTINEL (hazard ratio: 0.75, CI: 0.61-0.92, \( P = 0.007 \)) trials (Balcer LJ, Philadelphia, PA, S32.004).

Another aim of the AFFIRM and SENTINEL trials was to measure the effect of the medications on quality of life in patients with MS. The Multiple Sclerosis Quality of Life Inventory (MSQLI) and Visual Analog Scale (VAS) were used to measure quality of life and well-being, respectively. Patients on natalizumab therapy over 2 years in both the AFFIRM and SENTINEL trials demonstrated statistically significant improvement in quality of life and well-being compared to those on placebo or 30 mg interferon beta 1a intramuscularly weekly (Radick RA, Cleveland, OH, S52.005).

The incidence of neutralizing antibodies and their potential clinical effect were investigated in the AFFIRM and SENTINEL trials. Natalizumab is a humanized monoclonal antibody against VLA-4, an integrin receptor that blocks T cell egress from the circulation into the central nervous system. Over a 2-year period, 6% of patients in the AFFIRM trial were found by enzyme-linked immunosorbent assay to have positive antinatalizumab antibodies at more than 2 time points separated by at least 6 weeks ("persistently positive"). Patients with persistent antibodies demonstrated a reduced clinical benefit by 6 months and a higher incidence of adverse reactions from infusion (Calabresi PA, Baltimore, MD, S42.007).

The most severe adverse reaction associated with natalizumab is the development of progressive multifocal leukoencephalopathy (PML). To find predictors of which treated patients are at risk for developing PML, investigators compared the cerebrospinal fluid (CSF) cell counts in patients with MS treated with natalizumab, untreated patients with MS, patients with HIV, and patients with other neurologic diseases. Also, PCR for JC virus DNA was performed on the CSF and peripheral blood. The patients with MS on natalizumab therapy had a low CD4:CD8 ratio in the CSF similar to the patients with HIV, whereas untreated patients with MS and patients with other neurologic diseases had normal CD4:CD8 ratios. The CD4:CD8 ratio returned to normal in the treated patients with MS 6 months after discontinuing therapy with natalizumab. These results suggest that the lowered CSF CD4:CD8 ratio in treated patients was the result of the natalizumab giving a similar immunologic profile as patients with HIV. The effect of natalizumab on the CD4:CD8 ratio may be a risk factor for developing PML, but further research is necessary to test this hypothesis (Stuve O, Dallas, TX, S32.001).

A study of how glatiramer acetate dosing affects MRI included a randomization of 90 patients with RRMS to 40 mg subcutaneously per day or 20 mg subcutaneously per day. At 7, 8, and 9 months after treatment was begun, the 40-mg dose demonstrated a 38% reduction in enhancing MRI lesions compared with the 20-mg dose; this difference did not, however, reach statistical significance (\( P = 0.0698 \)). The adverse reactions were similar in both groups (Cohen JA, Cleveland, OH, S61.001).

Mitoxantrone treatment for progressive MS has been associated with the development of acute myelogenous leukemia. In one clinical center, among 111 patients with MS treated with mitoxantrone, 3 developed acute myelogenous leukemia. This was a higher incidence than the 0.25% previously reported (Lynn DJ, Columbus, OH, P01.074).

The mechanisms of action of FTY720, a new medication to treat MS, were demonstrated in several papers. FTY720 is an oral agent that binds with high affinity to sphingosine 1-phosphate receptors. The drug has already shown effectiveness in reducing MRI activity and relapse rate over a 6-month period in a phase II trial of 281 patients with RRMS. Patients in another study demonstrated decreases in their peripheral lymphocyte counts at both tested doses (1.25 mg and 5 mg orally per day) beginning at week 1 and lasting until week 24 (Schmidli H, Basel, Switzerland, S32.003).

In a murine model, FTY720 prevented peripheral lymphocytes from leaving lymphoid tissue, decreasing their transit into other tissues and into the central nervous system. In addition, the murine model showed that FTY720 prevented vascular endothelial growth factor-induced leakage across the blood–brain barrier (Brinkmann V, Basel, Switzerland, P03.175).

Another study of FTY720 administered 2 to 4 weeks after onset of experimental allergic encephalomyelitis in...
mice showed normalization of somatosensory evoked potentials within 2 weeks. Neurologic deficits in the animals were improved by 4 weeks and histopathologic studies at autopsy showed no active inflammatory lesions. If it shows significant efficacy in its phase III trial, FTY720 could potentially be the first oral immunomodulatory agent for MS (Foster CA, Vienna, Austria, P05.193).

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is a syndrome consisting of (usually bilateral) ON and transverse myelitis. According to the most recent diagnostic criteria, the brain MRI should be normal. However, recent studies have shown that patients with NMO may have some typical abnormalities on brain MRI. MRI abnormalities in the hypothalamus and periventricular area have been shown to colocalize with areas of aquaporin-4 (AQP4), the predominant water channel protein in the central nervous system. The NMO-IgG antibody binds selectively to AQP4. Studies have shown that AQP4 is most highly concentrated in the astrocytic foot processes forming the blood-brain barrier around the hypothalamus and the periventricular areas. A study looked at 130 patients clinically diagnosed with NMO whose serum was positive for the NMO antibody. Nine of these patients had abnormal T2 signal in the hypothalamic and periventricular areas corresponding the localization of AQP4, although no autopsy studies were performed to verify this histologically. Future studies will be needed to further elaborate the relationship of the aquaporin water channel protein with the MRI abnormalities and the clinical manifestations of NMO (Pittock SJ, Rochester, MN, S22.004).

The NMO antibody was studied in two small cohorts of children with clinical NMO. In one cohort, all 4 children (girls) were positive for the NMO antibody. Three of the patients had ON followed by transverse myelitis and 3 also had supratentorial lesions on MRI. One of the patients had lupus (Moem M, Dallas, TX, P05.045). In the second cohort, a retrospective analysis of patients with MS who presented between 2002 and 2005 found 3 who met the diagnostic criteria for NMO. Two were women; 2 tested positive for the NMO antibody with the serology on the third patient pending. Common findings were an initial presentation suggestive of acute disseminated encephalomyelitis and a significant clinical response to rituximab without significant side effects (McClinskey N, Huntington, NY, P05.198).

INTRACRANIAL HYPERTENSION

A small prospective trial of endovascular venous sinus stenting was reported in patients with intracranial hypertension secondary to dural venous sinus obstruction. Ten patients had papilledema, elevated CSF pressures ranging from 270 to 450 mm H-O, and venous sinus obstruction demonstrated by retrograde cerebral venography and manometry. After stent placement, all patients had reduced sinus pressures and normalized CSF pressures at 3 months. Four patients became asymptomatic, 5 improved, and 1 remained unchanged. At 6 months after the procedure, 7 patients had repeat venography that showed no stent thrombosis. Future larger trials of this intervention may validate it as another treatment option besides optic nerve sheath fenestration and ventricular shunting for patients who have dural venous sinus obstruction and whose elevated intracranial pressure is refractory to medical therapy (Donnet A, Marseille, France, S35.004).

The Useful Field of View test is a composite measure of visual attention that has been used mainly to predict driving abilities. It assesses the area from which one can extract visual information from competing visual stimuli using a brief glance without head or eye movement. The limits of this area are reduced by poor vision, difficulty dividing attention and/or ignoring distraction, and slower processing ability. A study of the Useful Field of View compared normal subjects with patients who had extrastriate lesions in the temporo-occipital ("what" pathway) or the parieto-occipital ("where" pathway) region. Both groups performed poorly compared with normal subjects but the test did not distinguish between the two patient groups (Philippi CL, Iowa City, IA, P01.032).

Data were presented on the benefits of vision restoration therapy (VRT) for patients with different types of field loss. In one study, 302 patients with field defects resulting from various etiologies (stroke, traumatic brain injury, ischemic optic neuropathy, tumor) were retrospectively evaluated by suprathreshold perimetry after 6 months of daily VRT. Treated patients were able to detect 17.2% more stimuli within their original field defect at the end of the 6 month period (P < 0.001) and improvements were seen in 70.9% of patients independent of variables such as the age or cause of the visual field defect (Sabel BA, Magdeburg, Germany, S48.008).

Another study reported the long-term stability of visual field improvement after VRT. Twenty-four patients with visual field defects from stroke or traumatic brain injury underwent VRT for 6 (15 patients) or 12 (9 patients) months and had follow-up suprathreshold high-resolution perimetry and standard near threshold perimetry an average of 46 months after completion of VRT. On average, the initial gains on either 6-month or 12-month protocols were maintained at follow up. This correlated with patients' subjective assessment of their performance on activities of daily living (Sabel BA, Germany, P01.033).

A report presented results related to improving medical student and resident training in performance of confrontation visual fields. The study surveyed neurologists and neuro-ophthalmologists on their preferred technique,
reviewed neurology and neuro-ophthalmology textbooks, and reviewed 120 charts on a medical consultation service. The clinicians and textbooks agreed on the importance of this task and on methods of testing. The chart review revealed little routine use of confrontation visual fields by trainees. Additionally, the homonymous hemianopias found by the attending physician on 2 patients were not elicited by the trainees. A more thorough study of how medical schools are teaching confrontation visual fields appears to be warranted (Glick TH, Boston, MA, P01.013).

RETINA
A possible association of patent foramen ovale (PFO) with retinal ischemia was presented. In a database of 158 patients with clinical episodes of cerebral or retinal ischemia and a PFO found on transesophageal echocardiography, 13 (8%) had cryptogenic retinal ischemia with no cause other than the PFO. Mean age was 57 years (range, 17–80 years). Eight (62%) patients had vascular risk factors. Seven patients had retinal infarcts of which 2 were bilateral. Six patients had transient monocular blindness. Five patients had prior or subsequent cerebral infarcts. One episode was present on awakening and the others occurred during daily activities. Five patients (38%) had symptoms develop at the time of Valsalva maneuver. The authors reasonably concluded that cryptogenic retinal ischemia may be caused by paradoxic embolization by a PFO. Support for this mechanism includes an absence of vascular risk factors in some patients, relatively young age, and symptoms occurring during activity (Thaler D, Boston, MA, P01.050).

Alpha-interferons have been associated with retinopathy. Two cases of patients with MS treated with betainterferons (one with INF-1b, one with INF-1a) were reported to have asymptomatic retinopathy consisting of cotton wool spots noted within 4 to 6 months of beginning therapy. One was taken off therapy with resolution of the cotton wool spots. Further reports are needed to determine if the findings are therapy-related or coincidental (Roberts JK, New York, NY, P01.076).

Recent reviews have reported permanent visual loss in retinal migraine (RM). This and other inconsistencies in prior reports prompted a review of the literature on RM to see whether reported cases meet the International Headache Society criteria of “at least two attacks of fully reversible monocular visual disturbance associated with migraine headache within sixty minutes of the visual event.” Only 7 cases had clinical manifestations consistent with RM and only 3 met the strict criteria of RM. The authors concluded that migraine as a cause of transient monocular blindness is rare. This is an important contribution, because many patients have visual loss diagnosed as migraine when other etiologies should be pursued (Hill D, Atlanta, GA, P01.035).

GENETICS
In a study of 35 Saudi patients with a presentation resembling Leber hereditary optic neuropathy (LHON) who had no family history of LHON, only 6 had the primary LHON mutations. Fourteen patients had novel nonsynonymous mtDNA changes. Sixteen of 19 patients had evidence of mitochondrial respiratory dysfunction. Further study will determine the pathogenicity of these mutations (Bosley T, Camden, NJ, EV5.003).

A patient with episodic ataxia, seizures, migraine, and alternating hemiplegia was found to have a heterozygous mutation in SLC1A3 not present in his asymptomatic parents and controls. The mutation alters an amino acid residue strictly conserved in all glutamate transporters and in all organisms (down to bacteria). The transporter is important in removing glutamate from the synaptic cleft. This adds an additional mutation to CACNA1A and ATP1A2 as causes of this syndrome (Wan J, Los Angeles, CA, EV4.006).

A study of mitochondrial ATP synthesis in skeletal muscles of patients with dominant optic atrophy (DOA) with or without the OPA1 gene mutation was reported. Using MR spectroscopy, the calf muscles were studied at rest, during aerobic exercise, and during recovery. Various mutations in the OPA1 gene were associated with deficits in ATP synthesis, but patients without OPA1 mutations were similar to controls. These data support the role of mitochondrial dysfunction in OPA1-related DOA (Lodi R, Bologna, Italy, EV5.002).

Nine patients with LHON with monocular visual loss for less than 6 months and normal visual function in the fellow eye were followed prospectively for up to 2 years in an open-label, nonrandomized pilot study of topical brimonidine purite as prophylactic treatment after first eye involvement in LHON. Despite normal visual acuity at baseline in all patients, 7 patients had minimal changes in the central visual field of the “uninvolved” fellow eye. All patients had subsequent deterioration of visual acuity, visual field mean deviations, and foveal sensitivity in the fellow eye. The earliest pattern of visual field abnormality was typically a cecocentral defect enlarging to become a central defect often with a superior or inferior predominance. The visual field defects in the two eyes of any given patient were remarkably similar. LHON may be a bilateral condition at onset more frequently than appreciated (Newman NJ, Atlanta, GA, EV5.004).

Although retinal ganglion cell loss is seen in DOA and LHON, the underlying defects are dissimilar. DOA is caused by mutations in OPA1, which encodes a mitochondrial dynamine-related GTPase implicated in maintenance of the mitochondrial network; LHON is caused by mtDNA mutations affecting complex I. Respiratory function and mitochondrial network were studied in fibroblasts from
patients with DOA and patients with LHON. Galactose medium forced mitochondrial respiration in LHON leading to loss of ATP content and ultimately to cell death. A perinuclear mitochondrial fragmentation, as typically seen in apoptosis, was also evident in LHON. The cell phenotype of DOA fibroblasts in galactose medium differed from LHON being mainly characterized by rearrangement of mitochondrial network and maintenance of cell viability (Careelli V, Bologna, Italy, EV4.001).

In a review of 74 patients with LHON mutations at positions 11778 and 3460, 54 had nonocular manifestations. These included an MS-like disorder, Parkinsonism, tremor, myoclonus, brisk deep tendon reflexes, syncope, hypotonia, migraine, epilepsy, psychiatric disorders, cramps, cardiology abnormalities, and other miscellaneous findings. There was no mutation or haplogroup-specific prevalence for any nonocular feature and no differences in serum lact acid levels. Mitochondrial proliferation was a compensatory change in skeletal muscle. Family clustering of 2 or more individuals with the same nonocular feature was frequently observed. Approximately half of patients with nonocular features were asymptomatic carriers (Morgia CL, Bologna, Italy, EV4.010).

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a syndrome of absent conjugate horizontal gaze and severe progressive scoliosis starting in infancy. The corticospinal tract and the dorsal column–medial lemniscal pathway fail to cross in the medulla in patients with HGPPS, contributing to deep fissures in the medulla with an abnormal butterfly-like appearance. Most patients have come from consanguineous kindreds. In a study of 3 nonconsanguineous families, distinct novel compound heterozygous ROBO3 mutations were found altering highly conserved residues or resulting in a premature stop codon. All newly identified mutations were located in the extracellular domains of ROBO3 and the majority of previously reported ROBO3 mutations (Jen JC, Toronto, Ontario, Canada, EV4.009).

A new genetic mutation for early-onset Parkinson disease was discovered in the gene for polymerase gamma (POLG-1). POLG-1 is a mitochondrial protein encoded in nuclear DNA, which has previously been implicated in progressive external ophthalmoplegia and infantile hepaticoencephalopathy Alpers syndrome. Two sisters were found to have a levodopa-responsive syndrome consisting of action tremor, bradykininesia, hypomimia, and stooped posture. Both sisters did not have either ptosis or any evidence of external ophthalmoplegia. This discovery adds to the breadth of clinical manifestations of POLG-1 mutations (Davidenzon G, New York, NY, S40.003).

**TACTILE PERCEPTION IN BLINDNESS**

Blindness is associated with superior tactile perceptual abilities. A functional MRI study examined the differences between 7 blind and 7 sighted subjects during an encoding/retrieval test of touching and recalling the pattern on sandpaper surfaces. Although the recognition memory scores were not significantly different, the blind subjects had activation of bilateral secondary visual areas (BA 18, 19), whereas sighted subjects activated the right inferior parietal cortex and left superior parietal area in both the encoding and retrieval tasks. Crossmodal plasticity may underlie superior tactile perceptual abilities in blind people (Dorsch A, Bethesda, MD, PO2.109).

**STROKE**

Intravenous tissue plasminogen activator (tPA) is used in treatment of ischemic stroke of 3 hours’ duration or less. An optimal patient for intravenous tPA is one with a stroke occurring within the hospital. A review of patients in one university hospital over 3½ years found that of 52 ischemic strokes occurring in the hospital, 35 had an absolute contraindication to treatment with tPA. Of the other 17, none received thrombolytic therapy mainly because of a delay in neurologic consultation and/or CT scanning (El-Zammar ZMK, Dorchester, MA, PO1.046).

Methamphetamine abuse has been reported as a cause of stroke. Possible mechanisms include acute hypertension, vascular toxicity, and vasculitis. Two cases of internal carotid artery dissection were reported in young women. Both had middle cerebral artery (MCA) distribution infarcts. No other risk factors were found (McIntosh A, Aliso Viejo, CA, PO1.066).

**EYE MOVEMENTS**

Prior studies have shown that the area around the intraparietal sulcus of the posterior parietal cortex is important in maintaining spatial constancy around saccades whenever nonvisual information (or efference copy) is required. To determine a perceptual correlate of this, post-saccadic localization of a target was studied in patients with right parietal lesions. During a visually guided saccade, the target was blanked for 200 msec and then displaced right or left. Subjects were asked to determine the direction of displacement. Normal subjects performed well and patients performed at chance in identifying the direction of target displacement. This study demonstrated that the perception of target displacement is impaired based on deficient use of efference copy (Heide W, Niedersachsen, Germany, EV4.007).

**VESTIBULAR DISEASE**

Fourteen patients with unilateral vestibular failure resulting from vestibular neurectomy performed optokinetic eye movements during functional MRI. Compared with controls, patients had less activation of area MT/V5
bilaterally. The authors proposed that this phenomenon may be an adaptive mechanism for eliminating oscillopsia in vestibular loss and may contribute to a decreased sensitivity for slow visual motion (Deutschlander A, Munich, Germany, EV4.003).

Three women with chronic exposure to JP-8 jet fuel developed vestibulopathy. They had chronic complaints of dizziness, headache, fatigue, and imbalance. The first patient had performed fuel-tank maintenance for the Air National Guard for over a decade. The second and third patients had worked for several years as administrators in a small, poorly ventilated building near the flight line. Exposure to toxic hydrocarbons was substantiated by the presence of n-hexane in human blood specimens and n-undecane, n-dodecane, n-tridecane, n-tetradecane, and toluene in the building carpet analyses. The probable states of JP-8 during exposure were vapor, liquid, and aerosol. Quantitative vestibular tests in 2 patients revealed markedly diminished caloric and rotational responses consistent with bilateral vestibular paresis. One patient demonstrated borderline low rotational responses and left caloric weakness. Bilateral vestibular loss may be caused by chronic exposure to JP-8 jet fuel (Robb MJA, Phoenix, AZ, EV4.008).

Nystagmus produced by head shaking ("head-shaking nystagmus" [HSN]) is a common finding in unilateral peripheral vestibulopathy. In a study of HSN in 16 patients with dorsolateral medullary infarcts (Wallenberg syndrome), 14 patients had HSN with a fast-phase ipsilateral to the lesion. This type of nystagmus was seen even in the 8 patients with spontaneous contralesional nystagmus. Visual fixation and baclofen treatment reduced the HSN. The authors proposed that the HSN is generated by asymmetric velocity storage as a result of impaired unilateral nodulovular inhibition on velocity storage (Choi K, Seongnam, South Korea, EV4.004).

A retrospective study looked at the prevalence of stroke among patients presenting to the emergency room with dizziness, vertigo, or imbalance. Among 1,666 patients identified over 2½ years, 53 (3.2%) were diagnosed with dizziness, vertigo, or imbalance. The first and third patients had worked for several years as administrators in a small, poorly ventilated building near the flight line. Exposure to toxic hydrocarbons was substantially by the presence of n-hexane in human blood specimens and n-undecane, n-dodecane, n-tridecane, n-tetradecane, and toluene in the building carpet analyses. The probable states of JP-8 during exposure were vapor, liquid, and aerosol. Quantitative vestibular tests in 2 patients revealed markedly diminished caloric and rotational responses consistent with bilateral vestibular paresis. One patient demonstrated borderline low rotational responses and left caloric weakness. Bilateral vestibular loss may be caused by chronic exposure to JP-8 jet fuel (Robb MJA, Phoenix, AZ, EV4.008).

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A new animal model for ocular MG used different HLA-transgenic mice (HLA-DQ8, DR3, and B6) to investigate variable susceptibilities to developing ocular MG after being immunized with an Escherichia coli plasmid expressing recombinant human AchR subunits. Some 89% of HLA-DQ8 mice and 65% of the HLA-B6 mice developed ocular MG, whereas only 3% of the HLA-DR3 mice were susceptible. Ocular MG was diagnosed by observing ptosis, ophthalmoplegia through videokerulography, and the absence of generalized weakness (Christadoss P, Galveston, TX, S36.003).

Pupillary abnormalities are not commonly reported in MG. However, research using infrared dynamic pupillometry demonstrated pupillary dysfunction in a cohort of 42 patients with MG as compared with 93 healthy control subjects. The reflex amplitude was smaller, constriction velocity was slower and latency was longer in patients than in control subjects ($P < 0.001$). The investigators also found that generalized, nontymectomized or symptomatic patients showed more significant differences in reflex amplitude constriction velocity and latency than did ocular myasthenics, thymectomized, or asymptomatic patients with generalized MG as compared with control subjects ($P < 0.001$). These findings suggest there is mild "laboratory" pupillary dysautonomia in MG, but no comment was made about whether the dysautonomia was clinically evident (Chenali KR, Cleveland, OH, P05.014).

MYASTHENIA GRAVIS

Approximately 10% to 15% of patients with generalized myasthenia gravis (MG) and 50% of patients with ocular MG are characterized as seronegative. To better define and characterize “seronegative” MG, all patients with MG examined over a 13-year period were retrospectively studied. Of the patients initially defined as seronegative with characteristic weakness and electromyographic findings and absent acetylcholine binding, modulating and striational antibodies, 17.4% converted to seropositivity on retesting 12 months later. Of those who remained seronegative, anti-MuSK antibodies were found in 38%. The authors proposed that the use of the term "seronegative MG" be reserved for patients with clinical and electromyographic findings consistent with MG who have persistently negative modulating, striatal, and binding acetylcholine antibodies and negative anti-MuSK antibodies for at least 12 months (Chan KH, Rochester, MN, S36.002).

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A review of repetitive nerve stimulation (RNS) results in subsets of patients with MG was performed. Results of RNS in the facial nerve and orbicularis oculi muscle were compared in patients with positive AChRab, positive anti-MuSK Ab, and negative in both. Sixteen MuSK Ab-positive patients were abnormal (89%), 93 AChRAb-positive patients were abnormal (59%) and 27 Ab-negative patients were abnormal (33%). For RNS with ulnar nerve stimulation, the MuSK group was abnormal 87.5% of the time, the AChRAb group 80% of the time, and the negative group 80% of the time. The findings on facial stimulation go along with the common clinical involvement of facial muscles in anti-MuSK-positive patients (Young AM, Birmingham, AL, P01.195).
HEADACHE

A prospective study of 141 patients with migraine (with and without aura) used transcranial Doppler to look for a right-to-left shunt as evidence of a PFO. This patient population was compared with 130 young (mean age, 33.8 years) and 200 older (mean age, 61.5 years) patients having sustained a stroke. A significantly higher incidence of PFO was found in patients with migraine with aura than without aura (51.7% vs 33.7%, P < 0.001). Interestingly, the incidence of PFO was also significantly higher in migraine with aura patients than in young (33.8%) and elderly (20.5%) patients having sustained a stroke. In patients with cryptogenic stroke, the incidence of PFO was 41.1% in the young and 25% in the elderly (Artal F, Brasilia, Brasil, P03.195).

The MIST trial was a prospective, randomized, double-blind, placebo-controlled study to test whether PFO closure with the STARFlex Septal Repair Implant vs a sham procedure would stop headaches in migraineurs with and without moderate to large intracardiac shunts as measured by transthoracic echocardiography. Selected patients had to have a minimum of 5 headache days per month and be refractory to prophylactic medications. The study found a 60.2% incidence of PFO in migraine with aura patients, 6 times greater than in the general population. Of the patients with shunts, 62.7% had a moderate-to-large-sized PFO. In this study, 74 patients were randomized to receive PFO closure and 73 to receive a sham procedure. The study failed to reach its primary end point of elimination of migraine headache. However, 42% of the patients treated with the PFO closure experienced greater than 50% reduction in headache frequency and the procedure was well tolerated (Dowson AJ, London, UK, S61.002). MIST 2, a larger prospective trial, recruiting patients in North America, will be starting soon.

NEUROSARCOIDOSIS

There were two reports of novel therapies for patients with refractory neurosarcoidosis. A case report was presented of a 40-year-old woman with progressive vision loss over several years and biopsy-proven sarcoidosis refractory to corticosteroids and cyclophosphamide. She developed worsening headaches, neck and back pain. A brain MRI showed leptomeningeal enhancement. The patient was started on 100 mg thalidomide per day and titrated up to 450 mg per day (higher doses caused excess sedation). The patient's vision stabilized and MRI enhancement was significantly reduced. The presenters noted that patients with pulmonary and cutaneous sarcoidosis have been reported in small case series to have clinical responses to thalidomide and suggested that this agent could be a potential treatment for neurosarcoidosis (Newton HB, Columbus, OH, P03.135).

A series of 14 patients with biopsy-proven neurosarcoidosis showed a positive response to therapy with infliximab. The patients had been refractory to corticosteroid treatment. After treatment with 5 mg/kg intravenous infliximab monthly for 3 to 6 months, 13 patients showed clinical improvement and 8 of 9 patients who underwent MRI scanning showed improvement on the scans. Only one patient had a significant adverse reaction (mild hypotension) (Aksamit AJ, Rochester, MN, P03.139).

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Horner Syndrome and Ipsilateral Abduction Deficit Attributed to Giant Cell Arteritis

We recently examined a 77-year-old woman with Horner syndrome and ipsilateral abduction deficit that we attribute to giant cell arteritis (GCA). This combination of findings has not been previously reported in GCA.

She had a history of hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, and colon carcinoma. Six weeks before presentation, she developed bitemporal headaches. She had stopped eating solids as a result of jaw claudication and had lost weight. She had diffuse myalgia and was unable to sleep well because of bilateral scalp tenderness. She noticed binocular horizontal double vision that was worse on left gaze and had experienced numerous episodes of blurring of vision in both eyes. Her family noted drooping of her left upper lid.

Neuro-ophtalmic examination revealed a best-corrected visual acuity of 20/40 in both eyes consistent with cataracts. Visual fields and color vision were normal. Left upper lid ptosis of 2 mm was present. In dim light, the right pupil measured 5.5 mm and the left 3.5 mm. In bright light, the right pupil measured 4.5 mm and the left 3 mm. Both pupils reacted briskly to light without afferent defect. Horner syndrome was confirmed by instilling 10% cocaine into both eyes (Fig. 1). (Hydroxyamphetamine was not instilled as a result of its unavailability.) Ocular ductions were full except for reduced abduction of the left eye. There was a 12 prism-diopter esotropia in primary position increasing to 20 on left gaze. The fundus examination was normal.

Temporal arterial pulsation was absent and the scalp was tender, but there was no thickening or nodularity. Westergren erythrocyte sedimentation rate (ESR) was 57, C-reactive protein was 4.1, and platelet count was 475,000. MRI of the brain with contrast was normal and magnetic resonance angiography showed an incidental small basilar tip aneurysm.

We made a diagnosis of GCA with concurrent Horner syndrome and left lateral rectus paresis. Intravenous methylprednisolone at a dosage of 250 mg per day and 80 mg oral prednisone per day was initiated. She was also started on alendronate, calcium with vitamin D, and ranitidine. Temporal artery biopsy on the left side was consistent with giant cell arteritis (Fig. 2).

Within a week of initiation of treatment, she had resolution of diplopia, headaches, and temporal scalp pain. Ptosis and pupillary abnormality remained unchanged. ESR, C-reactive protein, and platelet counts normalized in a week. Prednisone was tapered slowly over 18 months.

Horner syndrome resulting from GCA is very rare. Three cases of GCA and Horner syndrome have been reported in the English literature (1-3). Bell et al (1) reported a patient with GCA and Horner syndrome resulting from a brainstem stroke. Askari et al (2) reported a patient with internuclear ophthalmoplegia and Horner syndrome resulting from presumed giant cell arteritis. Bromfield and Slakter (3) reported a patient with GCA with postganglionic Horner syndrome. To our knowledge, no one has reported the combination of Horner syndrome and ipsilateral abduction deficit in GCA.

We were unable to perform the hydroxyamphetamine test to confirm the location of the lesion. The absence of brainstem and spinal cord signs and a normal brain MRI argue against a preganglionic location. Hollenhorst et al (4) suggested that paresis of different extraocular muscles at different times is the result of ischemia of the muscles or the nerve and not a brainstem lesion. Barricks et al (5) found extraocular muscle ischemia at autopsy in a patient with...
bilateral ophthalmoplegia resulting from GCA. Sibony and Lessell (6) reported aberrant regeneration in a patient with pupil-sparing third cranial nerve palsy resulting from GCA and suggested that ophthalmoplegia is neurogenic rather than myogenic. Meadows (7) suggested ischemia of vasa nervorum, whereas Martin (8) suggested ischemia of the extraocular muscles as the likely cause of diplopia in GCA.

In our patient, the combination of Horner syndrome and an ipsilateral abduction deficit suggests a cavernous sinus lesion. Within the cavernous sinus, the postganglionic sympathetic fibers travel with the sixth cranial nerve lateral to the internal carotid artery. Bromfield and Slakter (3) proposed that granulomatous inflammation of the internal carotid artery might directly involve the sympathetic fibers. We believe that the sixth cranial nerve in our patient could have been similarly affected.

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REFERENCES

Mydriasis and Accommodative Failure From Exposure to Topical Glycopyrrolate Used in Hyperhidrosis

We report a case of mydriatic pupils and accommodative failure caused by exposure to glycopyrrolate cream 0.5% (Robinul, Antigen Pharmaceuticals, Goldshield PLC, Croydon, UK) used in treatment of axillary hyperhidrosis. The connection was not realized until much later because no one thought to ask about the use of this agent. We are unaware of previous reports associating this agent with these findings.

A 19-year-old nursing student consulted her primary care physician for a 1-day history of blurred vision and heaviness in the left eye. There was no associated headache or other pertinent neurologic history. She had migraine and asthma and was using salbutamol inhalers. She denied the use of recreational drugs or any exposure to pharmacologic agents as a possible contamination source.

Ophthalmologic examination was normal except that the left pupil was dilated and did not constrict to light or a near target. Slit lamp examination was unremarkable; no sectoral paralysis or vermiform movement was noted. The pupil did not constrict after instillation of 0.125% pilocarpine. Neurologic examination was normal.

The mydriasis was attributed to migraine.

On two return visits, she was asymptomatic and the pupils were normal. However, she returned a fourth time with recurrence of symptoms. On that occasion, she had a fixed, fully dilated left pupil and a mid-dilated right pupil demonstrating some constriction to light. Neither pupil constricted after instillation of 0.125% or 4% pilocarpine.

On further questioning, we discovered that she had axillary hyperhidrosis and was regularly applying 0.5% glycopyrrolate cream before applying makeup. We reasoned that the pupil abnormality was the result of periocular contamination with the glycopyrrolate cream. After she stopped applying the cream, her pupils returned to normal within 1 week and she had been symptom-free ever since.

Primary hyperhidrosis is a disorder of excessive sweating. Treatment options range from antiperspirants or anticholinergics to iontophoresis, botulinum toxin injection, and thoracic sympathectomy in severe cases (1,2). The antimuscarinic properties of glycopyrrolate reduce sweating.

The mydriatic effect of 0.5% topical glycopyrrolate drops has been tested in animal eyes in which the pupil dilated within 5 minutes of application, reaching near-maximal levels by 15 minutes. These effects were faster, stronger, and more persistent than those of 1% atropine and lasted 1 week after initial application (3). The mydriatic effects of glycopyrrolate have also been demonstrated with its use as an anticholinergic agent in general anesthesia (4,5). However, to our knowledge, this is the first case demonstrating these effects with topical glycopyrrolate in humans. Physicians and patients should be aware of the potential side effects of mydriasis and accommodative failure with the use of topical glycopyrrolate and of the
importance of careful hygiene after its application so as not to contaminate the periocular skin or ocular surface.

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REFERENCES

Mechanism of Bitemporal Hemianopia

The article entitled “A Mechanical Theory to Account for Bitemporal Hemianopia From Chiasmal Compression” that appeared in the March 2005 issue of the Journal (1) has stimulated discussion among us. The “structural collapse theory” does not explain why neural transmission in the distorted nerve fiber may remain disrupted for many years yet be reversed in a matter of hours or days as seen in patients after decompression.

We suggest that the model may better explain the mechanism of injury in patients with traumatic chiasmal syndrome in which the bitemporal hemianopia is permanent. Various theories exist to account for the mechanism of injury in traumatic chiasmal syndrome (2–5), but none completely explains the relative sparing of uncrossed fibers. It has been suggested that a severe frontal head injury may cause separation of the skull in the midline with resultant sagittal tearing of the chiasm (2); however, not all injuries causing traumatic chiasmal syndrome are frontal. Rand (6) stated that the optic chiasmal nasal fibers are more prone to damage as they are “weaker.”

Perhaps a head injury produces intense, if brief, compression leading to selective disruption of crossing fibers, which lack the frictional support of contact with surrounding fibers as described in your model.

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REFERENCES

Authors’ Reply:

Our article is not trying to make claims of the material performance of nerve fibers. We were simply asserting that as a result of the concentrated loading experienced in the crossover nerve fibers, the tubes could “nip” and disrupt signals.

FIG. 1. A comparison of the different deforming actions of compression applied to crossing (perpendicular) and non-crossing (parallel) fibers. D, diameter of axon and length of nerve segment; p, proportion of circumference flattened by pressure (Reprinted from reference 1).
The degree of flattening has progressed to the point at which the area of contact between crossing and non-crossing cylinders is equal (see Figure 3).

“Elastic buckling” is a state in which the material remains within its elastic behavioral zone and, when unloaded, returns to its undamaged state. A good example would be a Bunsen burner tube.

We do not know the material properties of the nerve fiber well enough to be definitive. However, if it were elastic, we may expect retransmission of signals once the loading is removed provided the ionic link can be reestablished.

Furthermore, it cannot be presumed that nerve fiber malfunction occurs after the point of irreversible distortion/collapse. Indeed, the clinical recovery after chiasmal decompression would suggest that the point of nerve fiber malfunction occurs before irreversible distortion/collapse.

With increasing compression, the proportion of the circumference flattened will increase. The area of flattening will change from that in Figure 1 to that in Figure 2. The formula $\frac{1}{\pi} \times p$ (Fig. 1) dictates that if $p = \frac{1}{\pi}$, then the pressure difference between crossing and non-crossing cylinders is equal (Figs. 2 and 3). We proposed that it seems unlikely that the nerve fibers could adopt the configuration shown in Figures 2 and 3 without further collapse or malfunctioning. It seems quite possible that a nerve fiber that has adopted the shape in Figure 3 could spontaneously and relatively rapidly return to its normal shape.

Therefore, we see no reason why a physically distorted cylinder such as a nerve fiber should not return to its previous shape and achieve normal function within hours/days of cessation of a compressive force. In addition, there may also be an element of biologic repair.

REFERENCE

Principles and Practice of Behavioral Neurology and Neuropsychology


Scope: This is a multi-authored textbook about behavioral neurology and neuropsychology. The two editors are renowned researchers and clinicians who have thoroughly reviewed every aspect of behavioral neurology. The 92 contributing authors include not only neurologists, psychiatrists, psychologists, and neuroscientists, but also authors from internal medicine, radiology, rehabilitation, urology, oncology, pediatrics, public health, and law. This book is extremely valuable for anyone with an interest in behavioral neurology and neuropsychology.

The book is divided into seven sections, including 55 chapters, each giving an overview of a particular area. Although extremely detailed, it presents a pragmatic approach to cognitive, behavioral, and adaptive impairments caused by neurologic, traumatic, and medical disorders. The book begins with an overview of key issues in behavioral neurology and neuropsychology and covers a wide area of topics in 55 subsequent chapters. Except for 12 color plates placed at the beginning of the book, all illustrations are in black and white.

Strengths: The editors have brought together a wide group of contributors who have thoroughly reviewed every aspect of medicine relevant to behavioral neurology and neuropsychology. The writing is clear and the chapters are well organized with abundant tables and illustrations.

Weaknesses: The size of the book (1,168 pages) may dissuade readers who are looking for a quick piece of information. However, its clear organization and detailed index make it easy to use.

Recommended Audience: This book is extremely valuable for anybody with interest in all aspects of behavioral neurology and neuropsychology.

Critical Appraisal: The book was written by experts in behavioral neurology and neuropsychology who provide the most accurate and updated information on the diagnosis and management of behavioral changes in the setting of traumatic and nontraumatic disorders. Neurologists, psychiatrists, psychologists, pediatricians, and practitioners involved with rehabilitation or patients with chronic diseases should have this book on their desk.

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The Physiology of Cognitive Processes


Scope: This volume of predominantly original research rather than review papers represents the proceedings of a Discussion Meeting at the Royal Society in December 2001 with authors from Europe, the United States, and Mexico.

Strengths: Brought together in a single volume are 13 papers that illustrate the current boundaries in research into the physiology of cognitive processes, including sensation, perception, decision-making, attention, memory, the application of rules to guide behavior, and the use of sensory information to control movement.

Weaknesses: For most clinicians, the scientific complexity is overwhelming.

Recommended Audience: It is unlikely that any clinician will want to read this book from cover to cover. Many, however, will enjoy the opportunity to dip into its contents if only as a reminder of how far animal research has extended the forefront of scientific knowledge of cognitive processes.

Critical Appraisal: Unsuitable as a basic review of the subject, this book will, however, be of interest to neuroophthalmologists with a significant interest in basic science research. They might benefit from reading the chapters that, for example, expound the evidence that memory function may be widely distributed rather than localized to the temporal lobe, that distinct neural processes for the location of saccade targets and the generation of saccades are necessary to explain the flexibility of visually guided behavior, and that there is more than one area on the ventral surface of the occipital lobe involved in color perception.

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Orbital Tumors


**Scope:** This is a thorough exposition of the pathology, including pathogenesis, clinical, and investigation features, and treatment of ocular, orbital, and periorbital tumors. There are contributions from 30 individuals from around the world and extensive illustrations. It is aimed primarily at general ophthalmologists and oculoplastic surgeons as well as orbital specialists, but also is offered as a reference for pediatricians, radiologists, pathologists, neurosurgeons, and otolaryngologists.

The major sections deal with oncogenesis, diagnosis (including a helpful summary chapter on imaging in orbital differential diagnosis), and management of primary tumors, secondary tumors, pediatric tumors, and tumor-like conditions.

**Strengths:** The text is comprehensive with numerous well-illustrated cases. The first section on oncogenesis is a useful resource for clinicians unfamiliar with current knowledge of cancer biology, particularly with reference to orbital tumors. The section on diagnosis reiterates basic concepts of clinical assessment and investigation of orbital disease, including an enlightening discussion of new orbital imaging modalities. The sections on the various tumor types provide an easy-to-read exhaustive account of disease manifestations and management. The final section on management offers an overview of staging of orbital tumors, surgery, radiotherapy, and chemotherapy as well as developments in image-guided biopsy, surgery, and radiotherapy.

**Weaknesses:** Like many multi-authored texts, there is unnecessary, sometimes contradictory, duplication of material, inaccuracies when authors seem to stray outside their area of expertise, and inadequate indexing. It is unclear why there need be chapters on "Mass-Forming Inflammatory Lesions of the Orbit" and "Orbital Inflammation and Infection versus Neoplasia" or a chapter on "Neuro-Ophthalmologic Evaluation of the Orbit" after a chapter on "Clinical Evaluation of the Orbit." Amalgamation of these chapters would have been preferable. In one chapter, the authors depart from accepted practice in suggesting that total surgical excision is the recommended treatment of all meningiomas affecting the orbit, including optic nerve sheath meningiomas. The chapter on ultrasonography mainly details the pathologic and clinical features, the ultrasonographic characteristics being assigned to the legends, which are significantly more difficult to read. The annotations of some of the illustrations are too small.

**Recommended Audience:** This book will be a useful addition to the library of general ophthalmologists, oculoplastic surgeons, orbital specialists, and neuro-ophtalmologists as well as being a reliable reference for non-ophtalmologists.

**Critical Appraisal:** The book's strengths far outweigh its weaknesses. It is a generally well-written, well-illustrated, and comprehensive account.

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Ultrasonography of the Eye and Orbit, 2nd Edition


**Scope:** The second edition of this multi-authored ultrasound text is the long-awaited update to the authoritative reference that was first published in 1977. Although CT and MRI are the mainstays of orbital investigations, the text illustrates that adjunctive information and follow up can be obtained through ultrasound.

**Strengths:** The physics of ultrasound is presented in a readable fashion. The text clearly delineates the usefulness, reliability, and limitations of orbital ultrasonography. The book reviews newer ultrasound technologies such as power spectrum analysis, three-dimensional scans, very-high-frequency ultrasonic biomicroscopy, color Doppler imaging, and swept scans. Synopsis tables summarize important clinical information. The figures are of high quality, and the narrated dynamic ultrasound images on the accompanying DVD add use.

**Weaknesses:** Neuro-ophtalmologists would appreciate a separate chapter on color Doppler imaging and further ultrasound demonstrations of dysthyroid orbitopathy, orbital inflammatory syndrome, and arteriovenous fistulas. The text has few illustrations comparing the Ultrasound Biomicroscope (Zeiss-Humphrey Instruments, San Leandro, CA) with the anterior segment images obtained from the Artemis VHF ultrasound unit (Ultralink LLC, St. Petersburg FL). Migrated punctal plugs are an increasingly recognized problem and ultrasonic examples of this would be welcome.

**Recommended Audience:** The text is highly recommended as a general reference for all ophthalmologists...
and for neuro-ophthalmologists with an interest in orbital disease.

Critical Appraisal: The authors are well-published in the field of ultrasonography. The second edition of their ultrasonography text will be recognized as a benchmark reference.

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Atlas of Clinical Ophthalmology,
3rd Edition


Scope: This is a 764-page third edition of a phenomenal compendium of clinical images coupled with informative text. The first edition, published in 1984, is likely found in every ophthalmology library and many clinicians' personal libraries. A wonderful second edition followed in 1994. Now, 11 years later, the authors have compiled yet another outstanding edition. There are over 3,300 images—virtually all of high caliber—with over 1,800 in full color. There are external photographs, labeled line diagrams, slit lamp photographs, pathology slides, and electron micrographs to facilitate the illustration of various conditions. There are 28 contributing authors who have written on every topic of ophthalmology with helpful images of anatomy and ocular examination. They have taken extra effort to demonstrate to the reader that many eye conditions are often a reflection of systemic disease. They have similarly done a marvelous job of covering emerging technologies since the last edition, including wavefront analysis, optical coherence tomography, macular hole surgery, phacoemulsification surgery, and corneal refractive surgery.

Strengths: The images are colorful, informative, and representative of many ocular conditions. Almost every discipline in ophthalmology is equally represented. The authors have masterfully covered both local and systemic diseases. A useful CD-ROM includes all the images in digital format. The book is reasonably priced for such a large, high-quality color atlas.

Weaknesses: Some cross-referencing between individual chapters is required when readers are looking for the various ocular manifestations of a systemic condition.

Recommended Audience: This book belongs in every ophthalmology library and resident bookstore. It is a classic atlas supporting ophthalmology's claim as a strong visual specialty. The accompanying digital images on CD-ROM will be used by many residents in electronic presentations to depict clinical conditions.

Critical Appraisal: This is a masterpiece. The first edition was honored with the Best Medical Textbook of the Year award (1984) and is on the list of the 100 important ophthalmology books of the 20th century. The third edition simply builds on previous excellence. I will refer to this book frequently in teaching.

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Clinical Pathways in Neuro-Ophthalmology: An Evidence-Based Approach, 2nd Edition


Scope: This text provides a comprehensive overview of the vast majority of clinically important neuro-ophtalmic entities. Seven of the 20 chapters deal with optic nerve disease followed by a thorough discussion of other afferent and efferent neuro-ophtalmologic disorders. Two chapters are devoted to eyelid abnormalities and one to the pupil.

Strengths: The rubric “evidence-based medicine” describes the process by which clinical reports are currently evaluated, and it is this methodology that the authors apply to the subspecialty of neuro-ophtalmology. By attaching a metric to class of evidence (I-IV) and strength of treatment recommendations (A-U), the authors provide the reader a framework to evaluate why clinicians “do what they do” in virtually all clinically important neuro-ophtalmologic scenarios. In addition, diagnostic algorithms provide a useful overview of the clinical problem at hand to not become lost in the vast literature reviewed in this textbook.

Weaknesses: No illustrative material is provided. In many instances, such information (optic disc appearance, neuro-imaging findings) is critical in establishing the correct diagnosis. In addition, many of the tables are so comprehensive that they may be overwhelming for the reader in search of basic information.
Recommended Audience: This is not a book for the neophyte in neuro-ophthalmology, but for physicians with a strong interest and clinical passion for this subspecialty. The authors assume that the reader has a sound understanding of anatomy and physiology of the central nervous system and that localization of the disease process has been correctly established. The question-and-answer format is a useful way to help the reader understand what is most important in the clinical case at hand.

Critical Appraisal: This book is an important addition to the array of texts available in this subspecialty. Its unique approach is an important step in applying an evidence-based strategy to neuro-ophthalmology. It teaches the importance of critically reading the literature as a basis for formulating rational and appropriate diagnostic and therapeutic decisions.

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Handbook of Headache, 2nd Edition

Scope: This is a 400-page pocket book that reviews the diagnosis and management of headache. It is intended for primary care physicians, residents, and students.

The book begins with an introductory chapter on headache diagnosis and medicolegal issues, and then continues with 14 chapters on the diagnosis and treatment of specific headaches such as “posttraumatic headaches,” “chronic daily headache,” and “first or worst headaches.” Migraines are addressed in more detail with diagnosis, abortive, and preventive care handled in separate chapters. It concludes with chapters providing case presentations and discussion, a self-test, and patient resources.

A typical chapter begins with a short introduction on the identifying aspects of the particular headache and the International Headache Society classification. It continues with a differential diagnosis and suggested diagnostic testing. It concludes with treatment options. Chapters are well-referenced and include numerous tables of supporting data.

Strengths: The two authors, both neurologists specializing in headache, write with a single voice in approaching the diagnosis and management of headache. Important data are summarized in tabular form. Unlike many medical handbooks, it provides synopses of more rare syndromes. The authors offer specific recommendations for stepwise diagnostic testing and treatment, including medication dosages. They provide a range of treatments but highlight their personal experience with the pros and cons of each medication or modality. The index provides rapid access to the pertinent sections.

Weaknesses: Additional tables or flowcharts to guide an inexperienced clinician would have been useful.

Recommended Audience: Although the book is intended for primary care physicians and residents, it should also be useful for ophthalmologists who see patients with headaches. It does not have sufficient detail to be useful to neurologists.

Critical Appraisal: This book is a winner on two fronts: a solid reference text that is also practical.

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Upcoming Meetings

Sept. 10–Sept. 15, 2006
XVIth International Congress of Neuropathology
San Francisco, CA
http://www.icn2006.org

European Association for Vision and Research (EVER)
Vilamoura, Portugal
Contact: ever@ever.be

Oct. 7–Oct. 12, 2006
Congress of Neurological Surgeons 56th
Annual Meeting
Chicago, IL
http://www.neurosurgeon.org/meetings/2006/index.asp
Contact: cns@ntsmeetings.com

Oct. 8–Oct. 11, 2006
131st Annual Meeting of the American
Neurological Association
Chicago, IL
http://www.anuegoa.org
Contact: julieratzloff@llmsi.com

36th Annual Meeting of the Society for Neuroscience
Atlanta, GA
http://web.sfn.org/am2006/
Contact: info@sfain.org

Oct. 26–Oct. 29, 2006
Joint World Congress on Stroke
Cape Town, South Africa
Contact: stroke2006@klenes.com

Oct. 29–Nov. 3, 2006
XVII International Congress of Eye Research
Buenos Aires, Argentina
http://www.icer2006.com
Contact: icer_2006@yahoo.com

Nov. 11–Nov. 14, 2006
Joint Meeting
Annual Meeting of the American Academy of
Ophthalmology (AAO)
Asia Pacific Academy of Ophthalmology (AAPAO)
Las Vegas, NV
http://www.aao.org/aao/annual_meeting
Contact: meetings@aao.org

Nov. 29–Dec. 2, 2006
XVIth International Neuro-Ophthalmology
Society Meeting (INOS)
Tokyo, Japan
http://www.inos2006.jp
Contact: inos@inoue-eye.or.jp

Dec. 2, 2006
Japanese Neuro-Ophthalmology Society
Meeting (JNOS)
Asian Neuro-Ophthalmology Society Meeting (ASNOS)
Tokyo, Japan
http://www.inos2006.jp
Contact: inos@inoue-eye.or.jp

Jan. 18–Jan. 21, 2007
American Society of Neuroimaging
Miami, FL
http://asain.org
Contact: asm@llmsi.com

Feb. 7–Feb. 9, 2007
International Stroke Conference
San Francisco, CA
http://www.americanheart.org/portal/strokeconference/sc
Contact: strokeconference@heart.org

Feb. 10–Feb. 15, 2007
33rd North American Neuro-Ophthalmology
Society (NANOS) Annual Meeting
Snowbird, UT
http://www.nanosweb.org/meetings/nanos2007/
Contact: info@nanosnet.org

April 11–April 15, 2007
American Association of Pediatric Ophthalmology &
Strabismus (AAPOS) Annual Meeting
Seattle, WA
http://www.aapos.org/displaycommon.cfm?an=1amp;subarticlenbr=39
Contact: aapos@aaao.org

April 14–April 19, 2007
75th American Association of Neurological
Surgeons (AANS) Annual Meeting
Washington, DC
http://www.aans.org/annual/2006/meetings_dates_locations.asp
Contact: info@aans.org
April 28–May 5, 2007
59th Annual Meeting of the American Academy of Neurology (AAN)
Boston, MA
http://am.aan.com
Contact: membership@aan.com

May 6–May 10, 2007
Association for Research in Vision and Ophthalmology (ARVO)
Ft. Lauderdale, Florida
Contact: arvo@arvo.org

May 13–May 15, 2007
Society of Neurological Surgeons Annual Meeting
San Francisco, CA
http://www.societyns.org/meeting/index.html

May 26–May 29, 2007
European Neuro-Ophthalmology Society (EUNOS)
Istanbul, Turkey
http://www.eunos2007.org
Contact: info@eunos2007.org

May 29–June 1, 2007
European Stroke Conference
Glasgow, Scotland
http://www.eurostroke.org
Contact: hennerici@eurostroke.eu

May 31–June 3, 2007
XXVII Pan-American Congress of Ophthalmology (PAAO)
Cancun, Mexico
Contact: paa2007@servimed.com.mx

June 7–June 10, 2007
49th Annual Scientific Meeting of the American Headache Society
Chicago, IL
http://www.ahnaet.org
Contact: abxmtgs@talley.com

June 9–June 15, 2007
45th Annual Meeting of the American Society of Neuroradiology (ASNR)
Chicago, IL
http://www.asnr.org/asnr/upcomingmeetings.shtml
Contact: ltannehill@asnr.org

June 16–June 20, 2007
17th Meeting of the European Neurological Society
Rhodes, Greece
http://www.eufs2007.org
Contact: eufs2007@sallyjayconferences.com.au

July 12–July 17, 2007
IBRO World Congress of Neuroscience
Melbourne, Australia
http://www.ibro2007.org
Contact: ibro2007@sallyjayconferences.com.au

June 19–June 23, 2007
Canadian Congress of Neurological Sciences Annual Meeting
Edmonton, Alberta, Canada
http://www.ccns.org
Contact: web@ccns.org

August 25–August 28, 2007
11th Congress of the European Federation of Neurological Societies
Brussels, Belgium
http://efns2007.efhs.org
Contact: efns2007@kenes.com

June 28–July 2, 2008
World Ophthalmology Congress
XXXI International Congress of Ophthalmology
XII Chinese Ophthalmology Symposium
XX Hong Kong Ophthalmological Symposium
Hong Kong
http://www.woc2008hongkong.org
Contact: evawong@cuhk.edu.hk