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Harlequin Syndrome: Still Only Half Understood

William P. Cheshire, Jr MD, and Phillip A. Low, MD

Sympathetic vasodilatory and sudomotor fibers from the stellate ganglion mediate the principal reflex control of human facial thermoregulatory flushing and sweating (1,2). Heat stress, exercise, or sudden emotion in the patient with hemifacial cutaneous sympathetic denervation may elicit a dramatic alteration in facial appearance known as harlequin syndrome, in which a distinct line divides the denervated pale and dry half from the intact red and moist half. At rest, the only visible sign of sympathetic asymmetry may be oculosympathetic paresis, but this is not always present and, in fact, was not apparent in the first description of harlequin syndrome by Lance et al. in 1988 (3). Still other reports of this unusual syndrome have described tonic pupils, indicating a parasympathetic deficit. The literature lacks consensus regarding what, if any, pupillary abnormalities belong with the diagnosis of harlequin syndrome.

An article in this issue of the Journal of Neuro-Ophthalmology clarifies the relationship of pupillary abnormalities to harlequin syndrome. Bremner and Smith (4) report pupillographic findings in the largest published series of harlequin syndrome. Of their 39 patients from London’s National Hospital at Queen Square, 64% had abnormal pupils, most commonly Horner syndrome (46%) on the nonflushing side. They also found that the oculosympathetic deficit was almost always postganglionic.

Whereas harlequin syndrome is usually benign and imaging studies are unrevealing, it is worth noting that in this series 1 patient in whom topical hydroxyamphetamine indicated a preganglionic oculosympathetic deficit had been treated for an apical lung (Pancoast) tumor. Another 13% had tonic pupils with attenuated light responses, slow but exaggerated near responses with light-near dissociation, and sector palsy, and 2 patients had hypersensitivity to 0.1% pilocarpine. The tonic pupils had gone unnoticed by all but 1 patient. Sympathetic or parasympathetic pupillary abnormalities were bilateral in 15%, and combined sympathetic and parasympathetic deficits occurred in 7%. Of note, 23% had asymmetric or absent deep tendon reflexes, and 13% had signs of generalized autonomic failure.

Also in this issue, Galvez et al. (5) describe exercise-induced right hemifacial flushing and sweating in a patient with a left Horner syndrome. The interesting feature is that the starch-iodine test disclosed left hemifacial anhidrosis, and the sympathetic skin response, although intact on the right, was decreased in the left hand and abolished in the left foot.

Lance et al. (3) named this bipartite facial discoloration harlequin syndrome after the mischievous character in the Italian improvisational theater, the Commedia dell’Arte. Unlike some modern versions of Harlequin, which split his face into two colors, the original 16th century character’s mask was symmetrical and his costume was illustriously variegated in triangular patchwork (6). Accumulating evidence indicates that, like the original Harlequin’s irregular costume, the dysautonomia underlying harlequin syndrome is not always confined to the skin of the face but may be more widespread than previously recognized. Some cases of harlequin syndrome may be diffuse or patchy in their distribution, combining sympathetic and parasympathetic lesions (4) or facial and limb anhidrosis (5).
These detailed investigations, combined with previous anecdotal observations, indicate that harlequin syndrome overlaps with several other syndromes. Among them is Holmes-Adie syndrome, which is characterized by tonic pupils with asymmetric or absent tendon reflexes, as were found in five of the patients of Bremner and Smith (4). Harlequin syndrome has also been described in association with Ross syndrome, which is a partial dysautonomia comprising the clinical triad of unilateral or bilateral tonic pupils, segmental anhidrosis involving the face or body, and tendon hyporeflexia (7,8).

The detection of subclinical tonic pupils in a subset of patients with harlequin syndrome (4), as well as previous studies demonstrating subclinical anhidrosis in patients with Holmes-Adie syndrome (9,10), supports the conclusion that these syndromes may lie along the same nosologic spectrum. Alternatively, harlequin syndrome may simply be a highly visible final common dysautonomic manifestation of many disorders that asymmetrically target facial sympathetic vasomotor innervation, including occasionally Guillain-Barré syndrome, pure autonomic failure, multiple system atrophy, diabetic autonomic neuropathy, and neoplastic and traumatic lesions of the stellate ganglion.

The hypothesis advanced by Galvez et al. (5), that segmental dysautonomia might have reflected asymmetrical migration of neural crest cells during embryogenesis, would not account for the sudden appearance of symptoms during adulthood or the absence of heterochromia iridis. Harlequin syndrome is typically acquired, and the etiology of injury or degeneration of cholinergic ganglion cells or their postganglionic projections remains elusive. Perhaps harlequin syndrome results from regional depletion of a neurotrophic factor. Neurturin, for example, has been shown to be important for the maintenance of both parasympathetic (11) and sympathetic (12) cholinergic postganglionic neurons.

Harlequin syndrome might also result from regional infection by a neurotrophic virus. The pathogenic virus might have a preference for the stellate ganglion, as does herpes simplex virus for the geniculate ganglion in Bell’s palsy. Of interest, Ross syndrome has recently been described in a patient with acute cytomegalovirus infection (13), and tonic pupils have been reported as a complication of infection by varicella (14), parvovirus (15), and human herpesvirus 6 (16).

The elucidation of harlequin syndrome, it seems, has reached the halfway mark.

REFERENCES
Pupillographic Findings in 39 Consecutive Cases of Harlequin Syndrome

Fion Bremner, PhD, FRCOphth and Stephen Smith, MD, PhD

Background: Harlequin syndrome is a curious phenomenon in which one half of the face fails to flush during thermal or emotional stress as a result of damage to vasodilator sympathetic fibers. Anecdotal reports suggest that some of these patients have abnormal pupils. In this study we set out to systematically investigate autonomic pupil disturbances in an unselected cohort of patients with harlequin syndrome.

Methods: A consecutive series of 39 patients with harlequin syndrome who were referred to a tertiary autonomic function laboratory underwent slit-lamp examinations, testing of deep tendon reflexes, infrared video pupillography and, where needed, additional pharmacologic pupillary testing. Results were compared with a meta-analysis of all previously reported cases of harlequin syndrome (n = 39) identified from a literature search.

Results: In 65% of patients, no underlying causative medical disturbance could be identified. In 64% of patients, there were abnormal pupils, most commonly Horner syndrome, which was always present ipsilateral to the side of the face with impaired facial sweating and flushing. The lesion was postganglionic in 9 of 10 patients tested pharmacologically. Five (13%) patients had tonic pupils, most of whom also had tendon areflexia but no other neurologic findings, a pattern consistent with Holmes-Adie syndrome. In 2 of these patients, tonic and Horner pupils coexisted. Normal pupils were present in 36% of patients. These results are similar to those for the 39 previously reported patients with harlequin syndrome.

Conclusions: The frequent coexistence of harlequin and Horner syndromes without other neurologic deficits suggests pathologic changes affecting the superior cervical ganglion. Because either syndrome may occur alone, damage is apparently selective. Among the patients with harlequin syndrome who also have tonic pupils and tendon areflexia (Holmes-Adie syndrome), we postulate a ganglionopathy affecting not merely the (sympathetic) superior cervical ganglion, but also the (parasympathetic) ciliary and dorsal root ganglia. Because we found that more than 10% of patients had an undisclosed mass lesion in the chest or neck or a generalized autonomic neuropathy, we recommend a targeted evaluation in selected patients with harlequin syndrome.

In his original article, Horner (1) described reduced sweating above the eyebrow in patients with oculosympathetic paresis. Compared with sweating, the vasomotor control of cutaneous blood flow in the face is more complicated and is subject to a number of sophisticated control systems (2), of which sympathetically mediated active vasodilatation is only one. In 1988, Lance et al (3) reported a series of 5 patients in whom there was sudden loss of facial flushing on one side of the face after heat stress or exercise, resulting in a striking demarcation line between the reddened contralateral side of the face and the pale ipsilateral side of the face. They called this condition the “harlequin syndrome.” The authors demonstrated in 4 of these 5 patients that ipsilateral gustatory flushing/sweating was preserved and proposed that harlequin syndrome was caused by damage to the preganglionic sympathetic pathway. However, only 1 of their patients had Horner syndrome, implying that the lesion in the remaining 4 patients lay distal to the point of exit of the sympathetic pupillomotor fibers from the spinal cord, at level T2–T3 rather than T1.

There have since been a number of reports of harlequin syndrome [reviewed by Wasner et al (4)], and in some cases the patients also had a tonic pupil similar to that seen in the Holmes-Adie syndrome (5–8), implying concomitant damage to the postganglionic parasympathetic pupillomotor fibers. These reports have suggested that there is a nosologic relationship between Holmes-Adie syndrome...
HAS), which includes tonic pupils and tendon areflexia, Ross syndrome [HAS with patchy hypohidrosis (9)], and harlequin syndrome (7) and that both the parasympathetic and the sympathetic pathways may be affected in these conditions. Alternatively, the concurrence of these conditions may be coincidental.

The published literature on this topic is restricted to anecdotal case reports from which it is impossible to assess the frequency of concurrence of these different syndromes. Alternatively, the concurrence of these conditions may be coincidental.

We examined 39 consecutive patients with harlequin syndrome referred for autonomic function or pupillographic tests. There were 15 men and 24 women with a median age of 46 years (range, 10–74 years). The diagnosis of harlequin syndrome was confirmed by clinical observation of unilateral flushing after exercise-induced heat stress.

**Pupillography**

Slit-lamp examination of the iris, pupil, and anterior segment of the eye was performed. Pupil diameters and their responses to a bright flash of light (duration, 1.0
second) and an accommodative effort ("near response") were recorded in all but 1 patient by infrared video pupillometry. The pupil measurements were compared with a large normative database obtained from healthy age-matched control subjects. Sympathetic or parasympathetic deficits were diagnosed according to strict criteria as described in an earlier publication (10). One patient, a 33-year-old woman who was quadriplegic from Guillain-Barré syndrome with autonomic involvement, was too ill to undergo formal pupillography; her pupils were examined clinically at the bedside and photographed before and after eyedrop administration. Horner syndrome was diagnosed on the basis of redilatation lag [abnormally prolonged time for 75% recovery to baseline, T3/4, as defined in our previous publication (10)]. In patients with pupillotonia (which itself delays redilatation), the diagnosis of Horner syndrome rested on failure of pupils to dilate in response to cocaine. Tonic pupils were diagnosed on the basis of attenuation of the light response, a slow but exaggerated near response with light-near dissociation, by sector palsy, and in 2 patients, by denervation supersensitivity to topical 0.1% pilocarpine (10).

Pharmacologic Studies
Pharmacologic testing was used in a small number of patients in whom the diagnosis of a sympathetic or parasympathetic deficit was still unclear after standard pupillographic examination, in the patient too ill to undergo formal pupillography, and in patients in whom localization of the lesion causing Horner syndrome was needed. Tests of sympathetic integrity included topical 4% cocaine, 1% phenylephrine, or 1% hydroxyamphetamine. Dilute 0.1% pilocarpine was used to test for parasympathetic supersensitivity.

Deep Tendon Reflexes
Supinator, biceps, triceps, patellar, and Achilles tendon reflexes were examined in 30 patients by routine clinical testing.

Statistics
Differences between continuous variables were compared with Student’s t test and categorical differences by \( \chi^2 \) tests.

RESULTS
Underlying Medical Conditions
The medical diagnoses reached after investigation are shown in Table 1. In 10 (23%) patients, there were one or more causally related medical conditions: 2 brachial plexopathies caused at birth by forceps delivery, 2 pure autonomic failure (PAF), 1 multiple system atrophy (MSA), 1 Guillain-Barré syndrome, 1 unspecified dysautonomia, 1 apical lung (Pancoast) tumor (poorly differentiated adenocarcinoma treated by surgery and radiotherapy 4 years earlier), 1 thoric sympathectomy, and 1 type 1 diabetes (but with no evidence of autonomic neuropathy elsewhere). In the patient with MSA and in 1 of the 2 patients with PAF, the harlequin syndrome antedated the general autonomic failure by years.

In 5 (12%) patients, there were conditions only possibly causally related, including 1 patient with each of the following: discoid lupus erythematosus, trigeminal neuralgia, idiopathic bladder dysfunction associated with an unidentified lower spinal cord lesion, previous axillary surgery for hyperhidrosis, and repeated vasovagal attacks. In these last 2 patients, no definite abnormalities were found in a comprehensive battery of autonomic function tests. In 24 (65%) patients, no causally-related medical conditions were apparent.

Flushing and Sweating
The right side was affected in 17 patients and the left in 22. The extent of the phenomenon varied widely. In 22 patients only the face was involved; in 3 patients the neck was involved, and in the remaining 14 patients the trunk was involved, with or without effects in the arm or leg. Figure 2 shows an example of one of these patients. After exercise, the left side of his face failed to vasodilate (flush) or sweat in contrast with the normal right side, giving rise to a striking harlequin appearance.

Slit-Lamp Findings
Visible abnormalities of the pupil or iris when examined at the slit-lamp were found in 6 (15%) patients, including heterochromia iridis in the 2 patients with birth injuries, sector palsies in 2 patients with bilateral pupillotonia, and irregularly-shaped pupils without definite sector palsy in 2 patients with unilateral pupillotonia. In the remaining 33 patients, the pupils looked normal.

Pupillographic Findings
Twenty-five (64%) patients had abnormal pupils when examined pupillographically (Table 2). The most common abnormality was ipsilateral Horner syndrome, found in 18 (46%) patients. In 11 of these patients, this was the only abnormality. Three patients had additional parasympathetic deficits and 4 had bilateral Horner syndrome. Topical 1% hydroxyamphetamine testing, performed in 10 of the patients with a unilateral Horner syndrome (8 isolated and 2 with tonic pupils), disclosed a postganglionic lesion in 9 (90%). The only patient with a preganglionic lesion was the man with an apical lung (Pancoast) tumor.

Tonic pupils were found in 5 (13%) patients. The pupillotonia was bilateral in 2 and unilateral in 3...
In 1 of these patients, the diagnosis of tonic pupils had been made 25 years earlier. In the other patients, onset could not be determined as the pupillotonia was asymptomatic and had not been noticed by the patients or their referring clinicians. Supersensitivity to 0.1% pilocarpine was found in both of the patients in which this test was performed.

Evidence for combined parasympathetic and sympathetic pupillary deficits was found in 3 (7%) patients. An example is shown in Figure 3. This was a 63-year-old woman with ipsilateral Horner syndrome and a tonic pupil in the contralateral eye but with no evidence of a generalized dysautonomia. Of the 2 additional patients with combined parasympathetic and sympathetic deficits, one had the same pattern as shown in Figure 3, and the other had bilateral pupillotonia with an ipsilateral Horner syndrome.

Five (13%) patients had pupils that, although not definitely tonic or typical of Horner syndrome, were clearly abnormal. One of these patients, a 46-year-old woman, had an abnormal degree of anisocoria in the dark, the larger pupil being ipsilateral to the harlequin syndrome. This larger pupil showed no redilatation lag but had a relatively poor mydriatic response to topical cocaine compared with that for the other eye. A second patient, a 53-year-old woman, had equal but abnormally large pupils for her age on both sides; the pupil on the harlequin side also showed borderline redilatation times. A third patient, a 48-year-old woman, had abnormally small pupillary light responses without evidence of afferent visual pathway disease yet normal-amplitude brisk pupil constriction when viewing a near target. The 2 remaining patients, women aged 28 and 64, had abnormally large anisocoria both in darkness and in light. In both patients, the smaller pupil was on the same side as the harlequin syndrome, and light reflexes were attenuated with intact, brisk near responses. Pharmacologic testing in both of these patients showed symmetrically normal mydriatic responses to 4% cocaine but greater than expected miotic responses to 0.1% pilocarpine.

There was no pupillographic or pharmacologic evidence of either sympathetic or parasympathetic pupillary deficits in 14 (36%) patients with harlequin syndrome.

**Correlation of Pupil Findings With Other Neurologic Observations**

No relationship was found between the presence or absence of pupil abnormalities and the extent of the area affected by the harlequin syndrome. Nine patients had asymmetric or absent tendon jerks (Table 1), including the

---

### TABLE 1. Underlying medical diagnoses, pupil findings, and tendon jerks in 39 patients with harlequin syndrome

<table>
<thead>
<tr>
<th>I. Definite causally-related medical condition (n = 10)</th>
<th>No. cases</th>
<th>Pupil findings</th>
<th>Tendon jerks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth injury</td>
<td>2</td>
<td>H&lt;sub&gt;u&lt;/sub&gt; (2)</td>
<td>N</td>
</tr>
<tr>
<td>Pure autonomic failure</td>
<td>2</td>
<td>H&lt;sub&gt;b&lt;/sub&gt; (2)</td>
<td>N</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>1</td>
<td>H&lt;sub&gt;b&lt;/sub&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>1</td>
<td>T&lt;sub&gt;b&lt;/sub&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Idiopathic dysautonomia</td>
<td>1</td>
<td>H&lt;sub&gt;b&lt;/sub&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Pancoast tumor</td>
<td>1</td>
<td>H&lt;sub&gt;b&lt;/sub&gt;</td>
<td>N</td>
</tr>
<tr>
<td>Thoracic sympathectomy</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>II. Possible causally-related medical condition (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discoid lupus</td>
<td>1</td>
<td>T&lt;sub&gt;b&lt;/sub&gt;/H&lt;sub&gt;b&lt;/sub&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>1</td>
<td>H&lt;sub&gt;u&lt;/sub&gt;</td>
<td>N</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
<td>1</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1</td>
<td>A</td>
<td>N</td>
</tr>
<tr>
<td>Vasovagal attacks</td>
<td>1</td>
<td>T&lt;sub&gt;u&lt;/sub&gt;</td>
<td>A</td>
</tr>
<tr>
<td>III. No causally-related medical condition (n = 24)</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>H&lt;sub&gt;u&lt;/sub&gt; (6)</td>
<td>A(1); N(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H&lt;sub&gt;b&lt;/sub&gt; (1)</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T&lt;sub&gt;u&lt;/sub&gt; (1)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T&lt;sub&gt;b&lt;/sub&gt;/H&lt;sub&gt;b&lt;/sub&gt; (1)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A (4)</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N (11)</td>
<td>A(1); N(10)</td>
</tr>
</tbody>
</table>

N, normal; A, abnormal; H<sub>b</sub>, bilateral Horner syndrome; H<sub>u</sub>, unilateral Horner syndrome; T<sub>b</sub>, bilateral pupillotonia; T<sub>u</sub>, unilateral pupillotonia.
FIG. 2. Harlequin syndrome. A 56-year-old man shows post-exercise flushing and sweating restricted to the right half of the face. The pupils are normal.

patient with Guillain-Barré syndrome, all 5 patients who had at least one tonic pupil, 1 patient who had unilateral Horner syndrome, and 2 patients with normal pupils. Standard cardiovascular and thermoregulatory autonomic function tests showed widespread abnormalities in the 5 patients known to have generalized dysautonomia, but results were normal in all other patients with harlequin syndrome.

TABLE 2. Distribution of pupil findings in 34 patients with harlequin syndrome

<table>
<thead>
<tr>
<th>Parasympathetic deficit</th>
<th>Sympathetic deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>None</td>
<td>14</td>
</tr>
<tr>
<td>Unilateral deficit</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral deficit</td>
<td>1</td>
</tr>
</tbody>
</table>

Five patients were excluded from this analysis because although their pupils were abnormal, a definite diagnosis of sympathetic or parasympathetic deficit could not be made.

DISCUSSION

Our results are in general agreement with those in 39 previously reported cases of harlequin syndrome (3–8,11–28) (Table 3). Women seem to be more commonly affected than men, perhaps reflecting a greater propensity among women to seek advice for embarrassing asymmetry of facial flushing rather than any particular susceptibility of their sympathetic vasodilator fibers to injury. The median age at presentation was similar for men (47 years) and women (45 years) in our study and was consonant with the median presenting age (43 years) for women in the published literature. The median presenting age for men among published cases was significantly lower (21 years) than ours, perhaps owing to a disproportionate number of published cases in the pediatric literature.

Our study also agrees with the published literature in finding that the majority of patients with harlequin syndrome have abnormal pupils. The most common pupil abnormality is Horner syndrome, which was found in 46% of our patients and in 38% of previously reported patients. This finding is not surprising in view of the emerging evidence regarding the neural basis for harlequin syndrome. An active sympathetic vasodilator mechanism in the face has been demonstrated by Drummond and Finch (29) in 10 patients subjected to heat stress after stellate ganglion blockade. Most of these sympathetic vasodilator fibers leave the spinal cord at the level of T2–T3 (30) and travel up the sympathetic chain to terminate in the superior cervical ganglion. Postganglionic fibers are then distributed to the vascular beds of the upper and lower face via branches of
the internal and external carotid arteries, respectively. For much of their journey, these sympathetic vasodilator fibers travel alongside the sympathetic pupillomotor fibers and share susceptibility to damage from lesions in the chest and neck.

The lesion of harlequin syndrome has been localized in very few of the published reports, but we found that 9 of 10 patients with harlequin and Horner syndromes had postganglionic sympathetic pathway lesions. In all of these cases, the patients were otherwise healthy, and extensive investigations revealed no cause for the harlequin or Horner syndrome. In the absence of any evidence for a diffuse autonomic neuropathy, we assume these patients had focal lesions of the superior cervical ganglion.

Some 15% of our patients and some 26% of reported patients with harlequin syndrome cases had tonic pupils. The onset of the pupillary signs sometimes preceded the harlequin syndrome by as much as 25 years, although in most patients the precise temporal relationship cannot be established. Many of these patients with tonic pupils also had tendon areflexia and no other neurologic findings, suggesting a diagnosis of HAS. It is known that some patients with HAS also have evidence of patchy sudomotor dysfunction (9), so it seems that sympathetic ganglia can be affected as well as the dorsal root and other parasympathetic ganglia, raising the possibility that the concurrence of HAS and harlequin syndrome may be more than just coincidence. Thompson (31) estimated the prevalence of HAS in the population of Iowa at only 2 per 1,000. If a similar prevalence is assumed for the populations from which these patients with harlequin syndrome are drawn, then the rate at which we have observed both conditions together (equivalent to 206 per 1,000) is more than 100 times greater than expected by chance alone ($\chi^2 = 165.8; P < 0.001$ using Yates correction for continuity). Thus, it is likely that the etiologic agent responsible for HAS can also cause harlequin syndrome years or decades later in some patients. Given that the manifestations of HAS are associated with damage to ganglia, the site of damage in harlequin syndrome is likely to be the superior cervical ganglion. Such lesions may present as vasomotor (harlequin), sudomotor (Ross), or pupillomotor (postganglionic Horner) dysfunction, depending on the sensitivity of the tests used to examine the patient and other unknown factors.

In 5 of 39 patients in our series, the pupil examination was abnormal but did not meet our diagnostic criteria for a tonic pupil or Horner syndrome. It is likely that some of our pupil measurements lay outside the 95% normal limits by chance alone, but the relatively high frequency of observing these borderline cases and the findings of several variables outside the normal limits in each patient imply that in some patients there is a mild disturbance in autonomic innervation of the pupil. We intend to reexamine these patients after a few years to see if their pupils will become more convincingly tonic or show a definite Horner syndrome in the future.

In one third of our patients and patients in published reports, results of the pupil examination were entirely normal. It is possible that Horner syndrome was missed in some of these patients, as neither redilatation times nor pharmacologic tests have 100% sensitivity in detecting an oculosympathetic deficit. But such “missed” diagnoses probably account for only a few patients labeled as having normal pupils. In instances of “isolated” harlequin syndrome without other evidence of autonomic dysfunction, we must conclude that the lesion is small or the damage is selective to certain fiber populations within the sympathetic pathway. In our series, all 5 patients with generalized dysautonomia had abnormal pupils, although in 1 patient the deficits were parasympathetic rather than sympathetic. The rarity of diagnosing parasympathetic and sympathetic deficits in these patients may indicate the fact that autonomic disturbances are often patchy rather than diffuse in their distribution or may simply reflect the technical difficulty in unmasking a mild sympathetic deficit in the face of overwhelming parasympathetic denervation of the pupil (9,32).

Harlequin syndrome has previously been regarded as a curious but generally benign neurologic condition rarely associated with a serious underlying pathologic lesion.

### TABLE 3. Meta-analysis of pupil findings and underlying medical diagnoses in 39 previous reported cases of harlequin syndrome

<table>
<thead>
<tr>
<th>Pupil diagnoses</th>
<th>No. cases</th>
<th>Underlying medical diagnoses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horner</td>
<td>15</td>
<td>Anesthesia (12,13), paravertebral tumor (15), mass in neck (4,18), congenital (19)</td>
<td>3, 4, 12–20</td>
</tr>
<tr>
<td>Tonic</td>
<td>3</td>
<td>Multiple sclerosis (11)</td>
<td>7, 8, 11, 5–7</td>
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<tr>
<td>Horner + tonic</td>
<td>6</td>
<td>Central line (21), neck surgery (24)</td>
<td>3, 15, 21–24</td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>Parasyomnia (26), anesthesia (27), mediastinal neurinoma (28)</td>
<td>25–28</td>
</tr>
<tr>
<td>Not stated/not clear</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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Indeed, the overwhelming majority of patients in our series and in the published literature had no other neurologic or health problems. However, 3 of the patients in the published reports and 1 patient in our series had mass lesions in the neck or mediastinum. Furthermore, 5 of our patients had generalized dysautonomia, a high prevalence that may reflect the pattern of referrals to our institution, where we have a particular interest in these conditions. Of these patients with dysautonomia, 3 presented with harlequin syndrome before any other manifestations of an underlying neurologic disease had become apparent. Given this finding, it may be advisable in some patients with clinically isolated harlequin syndrome to arrange more detailed investigations of their autonomic and peripheral nervous systems or at least to keep them under surveillance.

Acknowledgments

I am deeply indebted to my co-author Stephen Smith, who had a great interest in these patients. He died last year before the conclusion of this study, but it was his enduring wish that I publish this case material. The pupillometry equipment was built with a generous grant from Fight for Sight.

REFERENCES

Horner Syndrome Associated With Ipsilateral Facial and Extremity Anhydrosis

Alberto Galvez, MD, Nadim Ailouti, MD, Agusti Toll, MD, Josep Maria Espadaler, MD, PhD, and Jaume Roquer, MD, PhD

Abstract: We report a patient with Horner syndrome together with anhidrosis affecting the ipsilateral face and extremities confirmed with starch-iodine and sympathetic skin response testing. No anatomic lesion was apparent. This is the first reported case in which Horner syndrome has been associated with such extensive hemibody sympathetic dysfunction in the absence of other neurologic findings. We propose a developmental disorder of neural crest migration as the cause.


A variety of focal eponymic dysautonomias have an association with Horner syndrome, including harlequin, Holmes-Adie, and Ross syndromes. The harlequin syndrome consists of unilateral facial anhidrosis and reduced facial flushing in the absence of Horner syndrome (1,2). It derives its name from the fact that under circumstances that would provoke sweating, the affected side of the face appears pale and the other side of the face appears red (the "harlequin sign") (3). Horner syndrome consists of unilateral ptosis and miosis with or without ipsilateral facial anhidrosis. The Holmes-Adie syndrome consists of tonic pupils and reduced deep tendon reflexes. The Ross syndrome consists of the harlequin syndrome together with the Holmes-Adie syndrome (segmental anhidrosis, tonic pupils, and hyporeflexia) (2,4).

Given the considerable overlap in these focal dysautonomic syndromes, there is probably a spectrum with differing mixtures of clinical manifestations (2). We report another overlap syndrome in a patient with unilateral Horner syndrome, ipsilateral facial anhidrosis, and ipsilateral extremity sympathetic dysautonomia confirmed with autonomic testing. We believe this to be the first reported case of Horner syndrome associated with such extensive dysautonomia.

CASE REPORT

Clinical Features

A 35-year-old man reported a 6-year history of episodes of flushing and sweating limited to the right hemibody after vigorous exercise such as running. He had earlier noted that his right pupil was larger than his left pupil. He denied any visual symptoms and was unaware of ptosis.

Ophthalmologic examination revealed a visual acuity of 20/20 in both eyes. External examination disclosed 1 mm of left upper lid ptosis with normal levator function. The right pupil measured 6.5 mm and the left pupil 4.5 mm in dim illumination. The right pupil measured 4.5 mm and the left pupil 4 mm in bright light and with near stimuli. There were no features of tonic pupil.

Results for the rest of the ophthalmic examination were normal. The neurologic examination was normal with the exception of a generalized hyporeflexia (all deep tendon reflexes were diminished to 1+). There were no sensory abnormalities and no postural hypotension. Results of brain and cervical-thoracic MRI were normal.

Autonomic Study Results

Topical Ocular Apraclonidine Test

Fifteen minutes after instillation of 2 drops of 0.5% apraclonidine into each eye, the right pupil measured 3.5 mm and the left pupil measured 4 mm ("reversal of anisocoria"). The left upper lid ptosis disappeared in favor of slight retraction (Fig. 1). In a separate testing session, 0.1% pilocarpine instilled into both eyes did not alter pupil size.

Starch-iodine Test

We induced sweating by asking the patient to climb a one-step stool several times. The sweating on the right side of the face induced violaceous flushing that was absent on the left side of the face. After application of yellow...
starch-iodine powder to both sides of the forehead, the right forehead skin color became dark blue whereas the left forehead remained yellow. This result indicated intact sudomotor function on the right forehead and absent sudomotor function on the left forehead (the rest of the face did not sweat sufficiently to show positivity on either side) (Fig. 1).

The Sympathetic Skin Response (SSR) Test

The SSR represents an electrical potential generated in skin sweat glands. In healthy subjects younger than 60 years of age, the response is always present throughout the skin of the extremities. It originates through a change in electrical skin resistance caused by skin humidity variation after a pulse of sweat. The SSR is most frequently used in diagnosing functional impairment of nonmyelinated postganglionic sudomotor sympathetic fibers in peripheral neuropathies. These fibers are the efferent component of the arc reflex and are activated by somesthetic afferent fibers that enter the spinal cord through the dorsal root and connect with Clark’s column. The sympathetic fibers reach the paravertebral ganglionic column by traveling through the anterior roots and nerves.

We applied a nociceptive sympathetic stimulus to the right median nerve at the wrist. A few minutes later, the same stimulus was applied to the left median nerve at the wrist. In a healthy person, the SSR should always be present throughout the skin of the extremities. However, in patients with peripheral neuropathies with impairment of nonmyelinated postganglionic sudomotor sympathetic fibers, the SSR will be abnormal, showing a malfunction of the entire autonomic nervous system or part of it. Responses were reduced after stimulation of both the left and the right median nerves (Fig. 2). The response was abolished in the left foot and decreased in amplitude in the left hand.

This phenomenon is explained by a reduction in the number of functioning sweat glands or sensory afferent fibers in the left extremities. The absence of a peripheral neuropathy on neurophysiologic tests rules out dysfunction of sensory afferent fibers. The most likely explanation is a reduction of excitability of the sympathetic arc reflex due to impairment of autonomic pathways.

Nerve Conduction Velocity Tests of the Median (Including F-wave), Ulnar, Tibial (Including H-reflex), and Sural Nerves

Results of these studies were within normal limits.

Cardiac Autonomic Reflex Tests

Measured by the heart rate variation (R–R interval) after stimulation by deep breathing, Valsalva maneuver, and postural changes (tilting), results of all studies were normal.

DISCUSSION

In our patient, topical pharmacologic testing confirmed a left Horner syndrome. Other autonomic testing
confirmed an ipsilateral facial and extremity anhidrosis. Parasympathetic function was normal.

He represents an exceptional case because of the extensive unilateral involvement of the sympathetic autonomic system (left face and left upper and lower extremities) combined with Horner syndrome. We have found only one similar case (5), a patient with “crossed” sympathetic dysfunction (left face and right arm). That patient did not have a Horner syndrome.

Caparros-LeFebvre et al. (6) reported a patient with Ross syndrome who had unilateral loss of facial sweating and contralateral extremity anhidrosis. That patient and ours probably lie on a spectrum of systemic-multifocal autonomic dysfunction observed in Holmes-Adie, Ross, and Guillain-Barré syndromes. Shin et al (7) reported 5 patients with Ross syndrome with pharmacologically confirmed Horner syndrome in 4. These 5 patients showed some degree of systemic autonomic dysfunction. In fact, the SSR was absent in both hands in 2 patients, absent in one hand in 2 patients (the Horner syndrome was ipsilateral to the hand deficit), and absent over the left anterior chest in 1 patient. The authors concluded that the autonomic dysfunction in Ross syndrome could be more extensive than the original description of Ross syndrome in 1958 (8).

The harlequin and Horner syndromes may be caused by structural lesions of the sympathetic autonomic pathways in the hypothalamus, brainstem, spinal cord, and preganglionic or postganglionic sympathetic nerves. There are many causes: iatrogenic (9-13), brain stem stroke (1), massive goiter with secondary sympathetic pathway compression (14), and mediastinal neurinoma (15). However, in many other patients there is no identifiable cause (2,3,5,7,11,16-19), as in our patient.

To account for cases in individuals without anatomically verifiable lesions, various explanations have been proposed. Lance et al (1) postulated a lesion of the anterior radicular artery in the spinal cord. Drummond et al (18) posited an autoimmune process without clear focality. Shin et al (6) proposed an embryogenic disorder of the neural crest affecting the migration of the derivative cells.

Our patient’s findings could be explained by a segmental dysautonomia caused by an autoimmune process. However, in that case we would expect involvement scattered on both sides of the body. For this reason, we postulate a developmental disorder of neural crest migration. In days 12–15 of embryogenesis, the neural crest, derived from the notochord, adopts a tubular disposition. At that time, the sympathetic cells become localized adjacent to the sulcus limitans on both sides of the basal plaque. A disorder of migration of neural crest cell derivatives at that time could explain an extensive alteration of the sympathetic system. This alteration of the sympathetic system would be unilateral if the migration disorder were localized to only one side of the basal plaque.

Several investigators (20,21) have studied the complex process of embryologic development of the sympathetic neurons derived from the neural crest with human embryonic stem cells (hESCs). This system can be used in the future for studying familial dysautonomia and other partial dysautonomias, helping to clarify the etiology of these overlapping syndromes.

In our patient, we cannot rule out an acquired dysautonomia of autoimmune origin, especially considering the patchy involvement of the left face and extremities.

REFERENCES


Postganglionic Horner Syndrome in Three Patients With Coincident Middle Ear Infection

Robert H. Spector, MD

Abstract: Three patients developed a postganglionic Horner syndrome during the course of an ipsilateral uncomplicated middle ear infection. The mechanism may be an effect on the middle ear caroticotympanic sympathetic plexus, for which there is considerable anatomic and physiologic evidence. Why Horner syndrome does not occur more often after middle ear infection is a mystery.


The most common causes of an acquired, isolated, non-traumatic, postganglionic Horner syndrome (PGHS) include cluster headache or a structural lesion of the internal carotid artery, such as a carotid artery occlusion, stenosis, dissection, or subcranial aneurysm, or an extrinsic mass that compresses the superior cervical sympathetic ganglion or the sympathetic nerves that exit from it (1). I report three patients who developed a PGHS in association with an ipsilateral uncomplicated middle ear infection.

CASE REPORTS

Case 1

A 43-year-old woman was reported by her primary care physician to have had a right middle ear infection in March 2006. Findings included hyperemia of the right tympanic membrane, dulling of the right tympanic light reflex, and a fever of 101°F. The syndrome resolved with 6 days of single antibiotic therapy.

Eight weeks later, she became febrile and complained of fever and pain in the contralateral left ear. Within 24 hours, her primary care physician found the same ear findings as had been noted on the opposite side, along with a fever of 100.6°F. The same antibiotic was prescribed. Within 12 hours after starting the medication, the patient's ear symptoms and fever began to subside. Later that evening, her family noticed that her pupils were unequal. The following morning, an ophthalmologist confirmed anisocoria and reported no other abnormalities on the ophthalmologic examination.

I examined the patient the same day (3 days after the onset of left ear pain). She offered no antecedent or recent history of nosebleeds, hemoptysis, dysphagia, anorexia, weight loss, facial pain, or numbness. Left ear pain was minimal. I did not examine the tympanic membrane. In subdued illumination, the right pupil measured 4.0 mm and the left pupil measured 2.5 mm. After direct light stimulation, each pupil constricted to 1.0 mm. Lids and facial moisture were symmetrically normal. The irides were isochromic.

Thirty minutes after instillation of 10% cocaine into each conjunctival sac, the right pupil had dilated to 6.5 mm and the left pupil had not dilated. An emergency MRA of the extra- and intracranial vessels and a soft tissue, noncontrast axial MRI of the cervical internal carotid artery showed no abnormalities.

Three days later, the anisocoria was unchanged. Lids and facial moisture were still symmetric. Topical instillation of 1% hydroxyamphetamine dilated the right pupil to 7.0 mm and the left pupil only to 3.0 mm. Several old photographs of the patient showed equal-sized pupils. Direct visualization of the nasopharynx by an otolaryngologist and a thin-section CT scan of the temporal and mastoid bones, with special attention to the middle ear cavity, gave normal results. One month later, the eye findings were unchanged.

Case 2

A 29-year-old man had had frequent middle ear infections during childhood, which, according to his mother, affected the right and left ears with equal frequency. The infections diminished after age 8 and his health was normal until his early 20s, when he had an uncomplicated ear infection that resolved with antibiotics. He could not remember which ear was affected, and medical records were not available.

In June 2003, he developed severe left ear pain with a noticeable asymmetry in the size of the pupils. On the second day of symptoms, his primary care physician recorded a temperature of 98.6°F and observed hyperemia of
the left tympanic membrane, obscuration of the left tympanic light reflex, left miosis (not measured), and questionable left upper lid ptosis. Treatment with a single oral antibiotic resolved the ear symptoms and signs, but the anisocoria and questionable ptosis persisted. Examination by an otolaryngologist was otherwise unremarkable.

I examined the patient less than a week after he had presented to his primary care physician. By then he was pain-free and afebrile. In subdued illumination, the pupils measured 5.0 mm in the right eye and 3.5 mm in the left eye. After bright light stimulation, both pupils constricted to 2.0 mm. The left upper lid was slightly ptotic. Facial moisture and facial sensation were symmetric. Corneal reflexes were equal. There was no palpable cervical lymphadenopathy. Topical instillation of 10% cocaine caused the right pupil to dilate to 7.5 mm but no dilation of the left pupil. MRA of the extracranial and intracranial vessels and a soft tissue axial MRI of the cerebral internal carotid artery gave normal results.

Three days later, the pupils were unchanged. After the topical instillation of 1% hydroxyamphetamine, the right pupil dilated to 7.5 mm and the left pupil dilated to 4.0 mm. Several childhood photographs of the patient showed equal-sized pupils. A thin-section CT of the temporal and mastoid bones, with special attention to the middle ear cavity, gave normal results. The patient subsequently had no ear symptoms, but the eye findings remained unchanged.

Case 3

A 7-year-old boy had the diagnosis of a left middle ear infection on January 21, 2006. A single antibiotic was prescribed. On the second day of treatment, he had noticeable left upper lid ptosis and unequal pupils. One day later, a pediatrician confirmed the findings and referred the patient to a pediatric otolaryngologist, who diagnosed a left Horner syndrome. No additional studies were recommended. An antibiotic was prescribed. The ear symptoms and signs readily resolved, but the eye signs persisted.

I examined the patient 2.5 weeks after the onset of symptoms. Left upper lid ptosis and miosis were present. In subdued illumination, the right pupil measured 6.0 mm and the left pupil 3.5 mm. After light stimulation, both pupils constricted to 2.5 mm. Left upper lid ptosis did not fatigue during prolonged upgaze. The topical instillation of a 1% hydroxyamphetamine ophthalmic solution caused the right pupil to dilate to 7.5 mm but the left pupil only to 4.0 mm. Facial moisture, facial sensation, and facial movement were symmetrically normal.

DISCUSSION

I have described one child and two adults who developed a PGHS during an ipsilateral and otherwise uncomplicated middle ear infection. All three patients showed miosis and preserved facial sweating; ptosis ranged from being not present to obvious. A sympathetically denervated iris dilator was supported by relatively sluggish dilation of the affected pupil in darkness and reduced dilation of that pupil after topical instillation of 10% cocaine. The postganglionic origin of this denervation was proven by lack of dilation after instillation of 1% hydroxyamphetamine. Despite timely and appropriate medical therapy of the ear infection, the eye findings persisted.

Preserved facial sweating with a PGHS can be explained simply by understanding the gross anatomy of the cervical sympathetic pathway. The ascending sudomotor sympathetic fibers, after synapsing in the superior cervical ganglion, course along the external carotid artery plexus and eventually join the ophthalmic division of the trigeminal nerve. A cervical sympathetic lesion distal to the carotid bifurcation, which would only involve the ascending pericarotid sympathetic fibers, would spare the sudomotor fibers that effect facial moisture.

The sympathetetic postganglionic fibers destined for the eye originate in cell bodies located in the superior cervical ganglion. Postganglionic sympathetic nerves ascend in the pericarotid plexus to join with the ophthalmic division of the fifth cranial nerve that carries them to the eye. Controversy exists regarding the presence, course, and function of branches of the ascending oculosympathetic nerves that branch off the pericarotid plexus and enter the middle ear. Their presence is indisputable in the rabbit, cat, dog (2,3), and human (4). Such fibers branch off the pericarotid plexus in the carotid sheath and pierce the posterior wall of the carotid canal, which also forms the anterior wall of the tympanic or middle ear cavity (Fig. 1).

According to Kobrak (5), the posterior wall of the carotid canal or anterior wall of the middle ear varies in thickness from dense bone to a membranous septum in which multiple dehiscences are present. Exactly what percentages of septa are thick, thin, or filled with dehiscences have never been quantified. But direct observations clearly show an array of nerve filaments penetrating the septum that merge into a plexus atop the promontory (or promontorium) of the middle ear, a prominent swelling on the floor of the petrous portion of the temporal bone. This plexus of nerve fibers atop the promontorium is made up of “caroticotympanic nerves.” De Kleijn and Socin (6) found “entire aggregates” of caroticotympanic nerves crossing the tympanic cavity in cats. Other investigators (4) have made the same observations in humans.

Frenckner (4) performed detailed surgical dissections of the exposed middle ear in living humans, believing that extirpation of the caroticotympanic nerves might resolve tinnitus or Ménière’s disease. Supplementing his operative observations are extensive anatomic studies in cadaver...
specimens. Using osmium-stained preparations and an operating magnifying microscope, he was able to visualize, describe, and illustrate the smallest nerve twigs within the tympanic cavity—their course, branching, and anastomoses. Observing wide variation, he noted that “they were never the same in two cases; some were fully exposed in an open sulcus, others were partially enclosed and a few were fully encased by a thick bony shell” (4).

Although the presence of a caroticotympanic plexus has been well established in several species, the autonomic function of this plexus is less certain. In cats, Barlow and Root (2) proved that these fibers carry autonomic nerve signals. These investigators isolated the superior cervical ganglion in eight cats and traced the ascending sympathetic fibers superiorly to the point where they entered the skull at the medial margin of the auditory bulla. The promontorium and overlying caroticotympanic nerves were identified and isolated. Electrical stimulation of the caroticotympanic nerves was followed by an immediate and striking dilatation of the ipsilateral pupil, whereas interruption of these fibers

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**FIG. 1.** The caroticotympanic sympathetic plexus. Filaments of the ascending postganglionic sympathetic nerves branch off the pericarotid plexus and pierce the posterior wall of the carotid canal. This wall also forms the anterior wall of the middle ear cavity. Lying atop the middle ear promontorium is an array of nerves called the caroticotympanic plexus. Note also that the vidian nerve in the vidian canal is formed by the confluence of the sympathetic nerve filaments from the middle ear and the greater superficial petrosal nerve, which branches off the facial nerve distal to the nerve to the stapedius muscle. (Modified from Reference 7.)
resulted in an absence of ocular changes upon subsequent stimulation of the cervical sympathetic trunk (2). In the five cats in which the caroticotympanic nerve fibers were surgically interrupted, the characteristic signs of a feline Horner syndrome developed: miosis, protrusion of the nictitating membrane, and, in some cases, narrowing of the palpebral fissure.

Although oculosympathetic paralysis and ptosis have not been described in patients who have had their caroticotympanic nerves manipulated, oculosympathetic paralysis has been reported, on rare occasions, in otitis media (7). Given the anatomy, it is surprising that this phenomenon is not encountered more often. The pathophysiology of Horner syndrome with middle ear infection could be attributed either to a change in the pressure dynamics or toxic inflammation of the septum that separates the carotid canal and tympanic cavity or to direct damage and scarring of the caroticosympathetic fibers in the middle ear.

Although the number of patients reported here is too small to allow firm conclusions, it is interesting that all had miosis, none had anhidrosis, and ptosis was either absent or obvious. Perhaps the branches off the carotid plexus that form the caroticotympanic plexus in the middle ear carry more signals to the pupillodilator muscles than to the eyelids. This report may raise more questions than it answers; however, it offers the opportunity to revisit the issue and consider whether middle ear disease should be included in the differential diagnosis of an acute-onset PGHS.

REFERENCES

Spontaneous Resolution of a Meckel’s Cave Arachnoid Cyst Causing Sixth Cranial Nerve Palsy

Maud Jacob, MD, Sachin Gujar, MD, Jonathan Trobe, MD, and Dheeraj Gandhi, MD

Abstract: A 32-year-old pregnant woman developed a progressive right sixth cranial nerve palsy as an isolated finding. Brain MRI disclosed a discrete lobulated lesion centered in the right Meckel's cave with intermediate signal on T1, high signal on T2, and diffusion characteristics similar to those of cerebrospinal fluid on apparent diffusion coefficient mapping. The initial radiologic diagnosis was schwannoma or meningioma. No intervention occurred. Shortly after cesarean delivery, the abduction deficit began to lessen spontaneously. One month later, the abduction deficit had further improved; 7 months later it had completely resolved. Repeat MRI after delivery failed to disclose the lesion, which was now interpreted as consistent with an arachnoid cyst arising within Meckel’s cave. Twenty-one similar cases of Meckel’s cave arachnoid cyst or meningocele have been reported, 7 found incidentally and 14 causing symptoms, 2 of which produced ipsilateral sixth cranial nerve palsies. All previously reported symptomatic patients were treated surgically. This is the first report of an arachnoid cyst arising from Meckel’s cave in pregnancy and having spontaneous resolution.

CASE REPORT

A 32-year-old woman in the 28th week of a normal pregnancy complained of binocular horizontal diplopia of 2 weeks' duration. On her initial examination, abduction of the right eye was reduced to 60%. Measurements of alignment showed a 10 prism diopter esotropia in primary gaze, worsening to 20 on right gaze and improving to 4 on left gaze. Results for the rest of the neuro-ophthalmologic examination were normal.

Examination 1 month later disclosed a complete lack of abduction in the right eye. At that time, she reported having experienced a 3-week episode of intense right periocular pain that resolved spontaneously. Otherwise, there were no neurologic manifestations.

Brain MRI performed without contrast injection because of her pregnancy showed a well-defined, lobulated, extra-axial lesion with its epicenter in the right Meckel’s cave. The lesion measured 11 mm anteroposteriorly and 6 mm transversely. It demonstrated intermediate signal intensity on T1 and high (fluid-like) signal on T2. On the ADC map, the lesion showed diffusion coefficient values similar to those of CSF (Fig. 1). The initial radiologic diagnosis was nerve sheath tumor (schwannoma) or, less likely, meningioma.

Ten weeks after the onset of diplopia, she underwent cesarean section delivery for fetal distress. The birth was otherwise normal. On the day after delivery, she noticed slight improvement in her diplopia. By 1 month after delivery, abduction of the right eye had improved to 70%, and there were no other findings. Seven months after delivery, she had had completely recovered normal ocular motility. A second MRI, performed with contrast medium at 1 month after delivery and 3 months after the beginning of her symptoms, failed to disclose the lesion (Fig. 2).
Head CT performed 3 months after delivery disclosed no erosion of the petrous apex. Based on the typical location of the lesion and its imaging characteristics, a diagnosis of an arachnoid cyst arising from Meckel’s cave was made in retrospect.

**DISCUSSION**

Our patient developed a right sixth cranial palsy during pregnancy that was associated with a cystic lesion in the right Meckel’s cave. After delivery, the sixth nerve palsy regressed, and at 1 month after delivery the lesion had vanished on MRI. Cystic lesions in that region have been given various names: Meckel’s cave arachnoid cyst (1,2), petrous apex cephaloceles (3–5), petrous apex arachnoid cyst (6–9), and arachnoid cyst involving the Gasserian ganglion (10). They are all cystic lesions centered in the posterior portion of Meckel’s cave that may expand into the petrous apex when they grow and erode the bone in this case. If the surgeon discovers a herniation of dura and arachnoid, the term “meningocele” is applied; if the cyst lining consists only of arachnoid, the term “arachnoid cyst” is applied (9). The arachnoid cyst may have herniated through a hole in the adjacent dura (10).

Eighteen cases of petrous apex arachnoid cysts have been studied previously by MRI (1–10,13). In two cases, imaging descriptions included only T2 imaging characteristics (2,5). Low T1 and high T2 signals have been found in all but one reported case (3,4,6–9), in which intermediate to high T2 signal was reported (7) (Fig. 3). Mild rim enhancement on postcontrast scans has been noted in

![FIG. 1. MRI performed during pregnancy. A. Precontrast T1 axial MRI shows a lesion in the right Meckel’s cave with intermediate signal intensity. B–C. T2 axial MRI shows a fluid-like high signal on T2. Note the prominent septations within the lesion (black arrows). D. Apparent diffusion coefficient map shows cerebrospinal fluid-like diffusion characteristics (arrow).](image1)

![FIG. 2. MRI performed 1 month after delivery. Precontrast T1 axial MRI (A), postcontrast T1 axial MRI (B), and T2 axial MRI (C) show that the Meckel’s cave lesion has vanished and that the cave now appears normal on both sides.](image2)
two cases (3,6) and no enhancement in five cases (3,4,7–9). Lobulation was described once (9). Similar to previous descriptions, the presumed Meckel’s cave arachnoid cyst in our patient had high T2 signal paralleling that of CSF. The only atypical feature in our patient was intermediate (rather than low) T1 signal. In all likelihood, the high T1 signal intensity in our patient derived from averaging of the septae within the lesion with the low T1 signal from CSF (Fig. 1C).

The diffusion characteristics of Meckel’s cave arachnoid cysts have not been reported previously, although they may be expected to be helpful. Arachnoid cysts, like the lesion shown in our patient, demonstrate a CSF-like signal, a clear distinction from epidermoid cysts, which also arise in this region and which demonstrate a diffusion signal of brain parenchymal intensity (11,12). In our patient, the initial imaging diagnosis was schwannoma or meningioma, although such a high T2 signal would not be consistent with either diagnosis. Lack of familiarity with this lesion, which has been infrequently reported, probably led to the error. Larger lesions have disclosed bone erosion (Fig. 4A), which was found on high-resolution temporal bone CT in all of the 10 patients in whom such a study was performed (3–10). Our patient lacked these findings, perhaps because the lesion was short-lived and relatively small (Fig. 4B).

The clinical features of similar cystic lesions arising from Meckel’s cave have been adequately documented in 21 cases (Table 1), including 15 women and 6 men with a mean age of 46 years (range 1.5–82 years). Seven of these 21 patients were asymptomatic (3,4,7–9), with brain imaging having been performed for symptoms unrelated to the lesion. Among the 14 symptomatic patients, 10 had manifestations related to cyst mass effect on adjacent structures (1–3,6–10) and 4 had manifestations related to a CSF fistula (3,5,7,13). Cyst mass effect was responsible for binocular diplopia in four patients [1 with third cranial nerve palsy (3), 2 with sixth cranial nerve palsy (1,3), and 1
<table>
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<td>Sixth cranial nerve palsy</td>
<td></td>
<td>Numbness</td>
<td></td>
<td>Diplopia improved, but not trigeminal numbness</td>
</tr>
<tr>
<td>Beck et al (1) (Case 12)</td>
<td>1.5</td>
<td>M</td>
<td>Sixth cranial nerve palsy</td>
<td></td>
<td></td>
<td>Ipsilateral exophthalmos</td>
<td>Normal examination 6 years later</td>
</tr>
<tr>
<td>Moore et al (3) (Case 3)</td>
<td>48</td>
<td>F</td>
<td>Third cranial nerve palsy</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wörner et al (2)</td>
<td>44</td>
<td>M</td>
<td>Transient diplopia</td>
<td>Dysesthesia</td>
<td></td>
<td>Transient vertigo</td>
<td>Lesion recurred 3 months after surgery; asymptomatic 15 months after second surgery. Trigeminal pain disappeared almost immediately; total right conductive hearing loss developed; headache and facial paresthesias improved but persisted; no lesion present on MRI 1 year after surgery</td>
</tr>
<tr>
<td>Achilli et al (6)</td>
<td>40</td>
<td>F</td>
<td>Pain, dysesthesia, and numbness (V1, V2)</td>
<td></td>
<td></td>
<td>Dizziness without vestibular dysfunction</td>
<td></td>
</tr>
<tr>
<td>Moore et al (3) (Case 4)</td>
<td>59</td>
<td>F</td>
<td></td>
<td>Pain (V1), dysesthesia, and numbness (V1, V3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jelsma et al (10)</td>
<td>58</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trigeminal anesthesia (V3) persisted, but dysesthesia subsided</td>
</tr>
<tr>
<td>Cheung et al (7) (Case 1)</td>
<td>46</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbamazepine eventually failed to control facial pain preoperatively; postoperatively, pain controlled with low-dose carbamazepine during 6-month follow-up</td>
</tr>
<tr>
<td>Chang et al (8) (Case 12)</td>
<td>9</td>
<td>M</td>
<td></td>
<td>Numbness (V1, V2, V3)</td>
<td></td>
<td>Headache</td>
<td>Trigeminal dysesthesia resolved after 6 weeks</td>
</tr>
<tr>
<td>Batra et al (9)</td>
<td>55</td>
<td>F</td>
<td></td>
<td>Pain (V1, V3), dysesthesia (V3), and numbness</td>
<td></td>
<td></td>
<td>CSF otorrhea resolved</td>
</tr>
<tr>
<td>Moore et al (3) (Case 2)</td>
<td>5</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motojima et al (5)</td>
<td>6</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache, vomiting, and rhinorrhea resolved</td>
</tr>
<tr>
<td>Hall et al (13)</td>
<td>33</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al (8) (Case 13)</td>
<td>70</td>
<td>F</td>
<td></td>
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<tr>
<td>Moore et al (3) (Case 5)</td>
<td>45</td>
<td>F</td>
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<tr>
<td>Moore et al (3) (Case 6)</td>
<td>82</td>
<td>F</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Moore et al (3) (Case 7)</td>
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<tr>
<td>Moore et al (3) (Case 8)</td>
<td>72</td>
<td>F</td>
<td></td>
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<tr>
<td>Moore et al (3) (Case 9)</td>
<td>66</td>
<td>F</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Moore et al (3) (Case 10)</td>
<td>36</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Srinivasan et al (4)</td>
<td>65</td>
<td>F</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; M, male; F, female.
with transient diplopia without any further details (2)], fifth cranial nerve dysfunction in 9 patients (2,3,6–10), exophthalmos in 1 patient (1), and vertigo in 2 patients (2,6). The lesion triggered a CSF fistula in four patients (3,5,7,13) when a tear occurred in the cyst wall, allowing CSF to leak into the petrous apex. Because the aerated petrous bone communicates with the middle ear, CSF otorrhea (2 patients) (3,13) or rhinorrhea (1 patient) (5) resulted. CSF fistula was also responsible for recurrent meningitis (1 patient) (5) and chronic otitis media (1 patient) (8). Five patients had headache (3,8), but whether it was caused by that particular lesion is uncertain.

Surgery was performed on all symptomatic patients (except 2, for whom treatment was not described (3,8) and on none of the asymptomatic patients. The surgical procedure was designed to collapse the cyst or to cure the CSF fistula or both. Diplopia improved after surgery in 1 patient (3) (Table 1) and had disappeared in 2 patients after 15 months (2) and after 6 years in another patient (1). For the remaining patient with diplopia, the outcome was not given (3). When the fifth cranial nerve was involved, the pain seemed to resolve postoperatively more often than the numbness (3,6,7,9,10). When described, the pain disappeared shortly after surgery. CSF fistulas finally resolved in all patients for whom an outcome was reported (3,5,13). In none of the seven asymptomatic patients was a follow-up examination reported, so the natural course of the lesion remains unknown. To our knowledge, ours is the first reported instance of the spontaneous resolution of a symptomatic Meckel’s cave arachnoid cyst.

Frequently found on imaging as an incidental finding, arachnoid cysts at any intracranial location may require surgical treatment when they enlarge and become symptomatic. On the basis of endoscopic observation of a suprasellar prepontine arachnoid cyst (14,15), a ball-valve mechanism is suspected to be the basis of enlargement. An alternative hypothesis is that cells lining the cyst wall continuously secrete fluid, which is then trapped (16).

Spontaneous disappearance of arachnoid cysts, as occurred in our patient, is rare in adults, with only one reported case in a 21-year-old patient (17). There are 13 reported cases in patients aged 16 years or younger (18–30). A provocative factor such as head trauma (20,29), meningitis (28), the Valsalva maneuver (31), coughing, sneezing, crying, or sporting activities (24,26,27,32) has sometimes been identified. Arachnoid cysts may progressively shrink without provocation or symptoms, a phenomenon observed in 9 patients (17–25) in whom the putative explanation is formation of a communication between the cyst and the subarachnoid space, allowing the cyst to drain through the normal CSF pathways. Whether there is direct transport through the cyst wall or whether CSF is released through a ball-valve mechanism is uncertain (24).

An alternative explanation for cyst disappearance, described in 5 patients (26–30), is sudden rupture into the subdural space, allowing fluid to spread and subsequently be reabsorbed. A subdural hematoma may sometimes initially accompany the subdural hygroma. In such cases, a tear in the cyst outer wall establishes a communication between the cyst and the subdural space (24,26,29). Supporting this hypothesis is the observation during craniotomy that a Valsalva maneuver caused a tear in the outer cyst wall (31). In our patient, the spontaneous resolution of the lesion occurred without any visible subdural effusion, even though the small size of the initial arachnoid cyst would have made it difficult to observe. The clinical improvement was concomitant with both the delivery and the lesion disappearance on MRI, suggesting the possibility that increased intra-abdominal or thoracic pressure during delivery may have been a triggering factor.

The discovery of a Meckel’s cave arachnoid cyst during pregnancy based on new symptoms raises the question of growth induced by the pregnancy itself (33–36). Three cases of intracranial arachnoid cyst have reportedly been diagnosed during pregnancy or the peripartum period because they had become symptomatic during those periods (33,34,36). The 2 patients who had become symptomatic during pregnancy (right hand tremor associated with headache in one and seizure in the other) underwent cesarean sections under general anesthesia to prevent the pushing efforts in delivery and to avoid increases in intracranial pressure by injection of anesthetic drugs into the epidural spaces (33,34). In the third case (36), the mother had a seizure 9 hours after delivering twins, and brain CT revealed a large medial fossa arachnoid cyst without any sign of rupture or hemorrhage into the subdural space. A fourth patient (35), known before pregnancy to have a posterior fossa arachnoid cyst, underwent cesarean section under epidural anesthesia and showed no change in cyst appearance in the peripartum period. An immunocytochemical study has shown progesterone receptors in the nuclei of cells lining the arachnoid cyst, suggesting an inhibitory influence of progestins on CSF absorption and evoking a similarity with hormone-dependent growth of meningiomas (37). We found no reported cases of Meckel’s cave arachnoid cysts discovered during pregnancy.

This case report describes a Meckel’s cave arachnoid cyst responsible for a sixth cranial nerve palsy during pregnancy and which spontaneously resolved after delivery. Because all of the previously described symptomatic patients had been treated surgically, this is the first reported instance of spontaneous resolution of both clinical and imaging findings. The imaging characteristics may vary
more than previously thought, including an intermediate signal on T1 and the absence of bone erosion in the petrous apex on CT. Pregnancy may have had a role in increasing the cyst size, and the pushing effort during labor may have triggered cyst rupture. Given the experience with this patient, arachnoid cysts should not be surgically treated during pregnancy unless they produce life-threatening manifestations.

REFERENCES

Arachnoid Cyst Causing Third Cranial Nerve Palsy Manifesting as Isolated Internal Ophthalmoplegia and Iris Cholinergic Supersensitivity

Lamees Ashker, MD, Joel M. Weinstein, MD, Mark Dias, MD, Paul Kanev, MD, Dan Nguyen, MD, and Dean J. Bonsall, MD, MS, FACS

Abstract: An 8-month-old boy presented with anisocoria, a sluggishly reactive right pupil, and cholinergic supersensitivity as the only signs of what proved months later to be compressive third cranial nerve palsy due to an arachnoid cyst. Tonic constriction and dilation, segmental iris sphincter palsy, aberrant regeneration phenomena, ductional deficits, and ptosis were absent. The initial diagnosis was postganglionic internal ophthalmoplegia attributed to a viral ciliary ganglionopathy. Nineteen months later, he had developed an incomitant exodeviation and a supraduction deficit. Brain MRI revealed a mass consistent with an arachnoid cyst compressing the third cranial nerve in the right interpeduncular cistern. Resection of the cyst led to a persistent complete third cranial nerve palsy. This is the second reported case of prolonged internal ophthalmoplegia in a young child as a manifestation of a compressive third cranial nerve palsy. Our patient serves as a reminder that isolated internal ophthalmoplegia with cholinergic supersensitivity is compatible with a preganglionic compressive third nerve lesion, particularly in a young child.

CASE REPORT

An 8-month-old boy was first noted to have anisocoria at age 3 months. He had been examined at a local hospital for an episode of lethargy and a viral illness had been diagnosed as the cause of anisocoria. An examining ophthalmologist suggested no further workup.

A second ophthalmologist examined him at age 8 months, finding that he was able to follow objects accurately with either eye. Versions were full, and he was orthophoric in all gaze positions with distance and near fixation. In darkness, pupils measured 6 mm in the right eye and 5 mm in the left eye. In room light, pupils measured 6 mm in the right eye and 3 mm in the left eye. There was no afferent pupillary defect. There was no segmental iris sphincter palsy and no vermiform iris movements. Testing for preserved pupil constriction to a near target could not be questioned this diagnostic hallmark, having shown that preganglionic third cranial nerve palsy may also demonstrate supersensitivity to dilute cholinergic agents (2–4). This discrepancy in pilocarpine testing is especially relevant in patients who present with isolated pupillary dilation in the absence of other neurologic signs. Traditionally thought to be indicative of benign processes, persistent isolated internal ophthalmoplegia can rarely be the sole manifestation of a third cranial nerve palsy (5–9).

We describe a patient in whom an arachnoid cyst compressed the third cranial nerve and produced a prolonged isolated internal ophthalmoplegia. Our patient is unusual in three respects. First, only one other reported case of compressive third cranial nerve palsy has persisted without ptosis or ocular motility dysfunction for longer than 1 year (5). However, in the patient of Wilhelm et al (5) the exact interval between isolated internal ophthalmoplegia and onset of diplopia is uncertain. Second, only one other such case has been reported in a young child, in which the interval between the identification of internal ophthalmoplegia and motility deficits was only 6 weeks (9). Third, there is no report of an arachnoid cyst causing these manifestations.

Supersensitivity of the iris sphincter to dilute cholinergic agents has long been considered diagnostic of a postganglionic third cranial nerve palsy (1). Recent studies have
performed owing to poor cooperation. There was no ptosis, and there were no signs of aberrant regeneration involving the eyelids or pupil. Results of the remainder of the examination were normal with the exception of mild myopia of 0.50 diopter in both eyes. Testing with 0.125% pilocarpine revealed marked constriction of the right pupil to 3 mm and no change in pupil size in the left eye, an indication of cholinergic supersensitivity in the right eye.

The patient was diagnosed of isolated postganglionic internal ophthalmoplegia due to viral illness. A pediatric neurology consultant found no abnormalities.

The patient was reexamined ophthalmologically at age 14 months without a change in findings. Nineteen months later, when he was 27 months old, his mother noted that the right eye had been turning out intermittently over the past month and that he had an apparent aversion to light with frequent closure of the right eye. Examination at that time revealed full versions but a 10 prism-diopter intermittent exotropia in primary and left gaze positions with distance and near fixation. He was orthophoric in right gaze and had a slight left face turn. There was a dilated right pupil with anisocoria greater in light than dark. Instillation of topical 0.125% pilocarpine again showed cholinergic supersensitivity of the right pupil.

He was diagnosed with an intermittent right exotropia with strabismic amblyopia, possibly exacerbated by defocusing due to accommodative insufficiency accompanying his right internal ophthalmoplegia. He was treated with 0.125% pilocarpine in the right eye to aid accommodation and to minimize blur that would result in amblyopia and patching of the left eye 4 hours daily to reduce amblyopia.

On reexamination when he was 28 months old, the exotropia had increased to 20 prism-diopters, and there was a question of slightly reduced supraduction-in-adduction of the right eye attributed to a previously unrecognized Brown syndrome. The increase in the exotropia was attributed to poor compliance. Results for the remainder of the examination were unchanged.

On reexamination when he was 31 months old, the exotropia was slightly decreased and a supraduction-in-adduction deficit was not noted. At ages 32 and 35 months, examinations disclosed that visual acuity was 20/40 in each eye by Lea optotypes. Versions were again full, and an exophoria was measured at 10 prism-diopters in distance fixation and 10 prism-diopters in near fixation.

On reexamination when he was 37 months old, his mother reported increased frequency of the exotropia over the past week. Visual acuity was 20/25 in each eye. There was a 14 prism-diopter intermittent exotropia in primary position with a definite supraduction-in-adduction deficit in the right eye with resultant left hypertropia in left gaze. There was no ptosis, and results of a pupillary examination were unchanged. Cholinergic supersensitivity of the right pupil to dilute pilocarpine was again demonstrated. Neither preservation of pupil constriction to a near target nor segmental sphincter palsy was noted. Signs of aberrant reinnervation involving the pupil or lid were not detected. A pediatric neurologic examination again showed no other abnormalities.

Brain and orbit MRI, obtained for the first time, showed an arachnoid cyst compressing the third cranial nerve within the right interpeduncular cistern (Fig. 1). Craniotomy showed that the arachnoid cyst was densely adherent to the third cranial nerve. Postoperatively, the patient immediately developed a complete right third cranial nerve palsy. He subsequently underwent strabismus surgery at age 5, consisting of a right medial rectus recession of 6.75 mm and a right lateral rectus recession of 8.5 mm with ½ tendon width supra-placement, producing a 20 prism-diopter exotropia in primary position at distance and near fixation. At age 7, his visual acuity was 20/50 in the right eye and 20/20 in the left eye.

DISCUSSION

Our patient was seen at age 8 months with isolated internal ophthalmoplegia and pupillary cholinergic supersensitivity. At age 27 months, he developed a small intermittent exotropia and a supraduction deficit that led to the diagnosis of a third cranial nerve palsy attributed to compression by an arachnoid cyst in the interpeduncular cistern. The persistent isolated internal ophthalmoplegia accompanied by cholinergic supersensitivity had originally been misdiagnosed as a postganglionic (ciliary ganglion or ciliary nerve) lesion, presumably of postviral origin.

Isolated internal ophthalmoplegia has many causes. In a patient with head trauma, biopsy demonstrated segmental tearing of fibers on the medial aspect of the third cranial nerve (10). There have also been several reports of nontraumatic persistent and isolated (or nearly isolated) internal ophthalmoplegia, with or without cholinergic supersensitivity, in otherwise healthy patients who later developed more complete third cranial nerve palsies owing to compressive lesions (5–9). Most of these patients have had intracranial aneurysms, and they often reported persistent headache. Other signs of third cranial nerve or other neurologic dysfunction usually followed. In patients with tentorial herniation, more complete third cranial nerve palsy and other signs of neurologic dysfunction, including mental status changes and hemiparesis, have usually followed within hours (11).

Wilhelm et al (5) reported a 33-year-old woman in whom isolated internal ophthalmoplegia was initially diagnosed as an Adie tonic pupil, followed 14 years later by other signs of third cranial nerve dysfunction, leading to...
the eventual diagnosis of a neurinoma of the third cranial nerve. Their patient had asymptomatic anisocoria and was found to have light-near dissociation, vermiform iris movements, and cholinergic supersensitivity. She returned with the complaint of diplopia 14 years later. No ophthalmologic examinations occurred in the interim between presentation and diagnosis 14 years later. At that point, the affected pupil measured 9 mm in darkness, there was pupillary areflexia to light and near stimuli, and incomplete ipsilateral impairment of adduction, supraduction, and infraduction, as well as ptosis with aberrant regeneration involving the lid. This patient differs from ours in four respects. First, the patient was an adult. Second, the patient had light-near dissociation. Third, the patient had more extensive signs of third cranial nerve palsy when the correct diagnosis was made 14 years later. The ophthalmoplegia may well have evolved over several years as its duration was uncertain. Fourth, the cause of the third cranial nerve palsy was a neurinoma, an intrinsic lesion, rather than an arachnoid cyst, an external compressive lesion, as in our patient.

Werner et al (9) reported a 10-month-old infant with anisocoria and internal ophthalmoplegia as the only signs of third cranial nerve compression by a cisternal endodermal cyst. The patient also demonstrated cholinergic supersensitivity. Light-near dissociation and segmental sphincter palsy were not reported. As in the patient of Wilhelm et al (5), Adie tonic pupil was incorrectly diagnosed. Unlike our patient, however, results of brain MRI and CT studies (not displayed in the report) were initially reported as normal. After an interval of only 6 weeks, the infant developed impaired adduction, supraduction, and infraduction of the affected eye. Aberrant regeneration involving the lid or pupil was not described. A repeat brain MRI demonstrated a cystic mass adjacent to the cisternal portion of the third cranial nerve. The resected mass was a neurenteric cyst. Like our patient, this infant had significant residual third cranial nerve palsy requiring multiple strabismus procedures. This patient differed from ours, however, in that the third cranial nerve palsy evolved much more rapidly. The interval between presentation and correct diagnosis, based on new signs of external ophthalmoplegia, was only 6 weeks, in contrast to 19 months in our patient. That patient also differed from ours in that CT and MRI failed to demonstrate the compressive lesion at the time of presentation.

Our patient’s delayed diagnosis was based on the presumption that the finding of isolated internal ophthalmoplegia and cholinergic supersensitivity precluded a preganglionic lesion. However, Jacobson (2) had earlier described cholinergic supersensitivity to 0.1% pilocarpine in 9 (69%) of 13 patients with preganglionic third cranial nerve palsies. The presence of supersensitivity was not related to the cause of the third cranial nerve dysfunction or

FIG. 1. Brain MRI performed 29 months after original presentation. A. T2 axial MRI demonstrates round high signal (arrow) in the right interpeduncular cistern compressing the cerebral peduncle in the course of the right third cranial nerve. B. Precontrast T1 sagittal MRI shows the cyst (arrow) in the region of the right third cranial nerve. C. Precontrast T1 coronal MRI shows partial effacement of the right interpeduncular cistern by the arachnoid cyst (arrow). D. Postcontrast T1 coronal MRI shows slight rim enhancement of the cyst.
to the time between onset and testing, but it was related to the extent of associated iris sphincter palsy and to the extent of anisocoria. Unlike our patient, some of Jacobson’s patients with long-standing preganglionic third cranial nerve palsies had other features usually attributed to postganglionic damage, including light-near dissociation and segmental iris sphincter palsy. He attributed the cholinergic supersensitivity to transsynaptic degeneration of postganglionic fibers in chronic preganglionic third cranial nerve disorders.

In a later prospective study of several patients with congenital, ischemic, compressive, and traumatic third cranial nerve palsies, Jacobson (3) found cholinergic supersensitivity to pilocarpine with all causes except ischemia. He concluded that a large, poorly reactive pupil supersensitive to pilocarpine does not exclude a preganglionic lesion. In a further study comparing the degree of cholinergic supersensitivity in patients with preganglionic and postganglionic third cranial nerve palsy, Jacobson and Vierkant (4) found that the degree of cholinergic supersensitivity is similar regardless of the site of injury.

Several other studies have demonstrated cholinergic supersensitivity of the iris sphincter in patients with preganglionic lesions (12–16) (Table 1). Other pupillary findings classically associated with postganglionic lesions, including light-near dissociation, segmental palsy, and a tonic response, have been documented in some patients with preganglionic third cranial nerve lesions (2,12–16). It therefore seems that all of the “classic” pupillary signs traditionally associated with postganglionic palsy may appear, either alone or in combination, in patients with preganglionic lesions.

The mechanisms producing tonicity, segmental palsy, and light-near dissociation are probably independent of cholinergic supersensitivity. Although Wirtschafter et al (17) postulated that the tonic near response in Adie pupil results from intracameral release of acetylcholine, there is no direct experimental evidence for this phenomenon. The tonic near response seems better explained by aberrant reinnervation.

Segmental sphincter palsy is ascribed to sectoral innervation of the sphincter by the short posterior ciliary nerves. Supporting evidence for this mechanism is also provided by the existence of sectoral corneal hypesthesia in many patients with Adie syndrome (18). However, sectoral denervation could occur with limited damage to fascicles of the preganglionic third cranial nerve even though there is no direct evidence for such a segmental organization in the preganglionic portion of the nerve.

Light-near dissociation in Adie syndrome has been attributed to aberrant reinnervation of the iris sphincter by misdirected postganglionic fibers intended for the ciliary muscle (1). This mechanism seems plausible because postganglionic axons intended for the ciliary muscle outnumber those intended for the iris sphincter by about 20:1 (19). However, aberrant reinnervation of the sphincter has also been documented in patients with compressive preganglionic third cranial nerve palsy, in whom sphincter contractions occur in synchrony with eye movements (20).

The mechanism of cholinergic supersensitivity in patients with preganglionic third cranial nerve lesions is not well understood. However, Jacobson (2) argues that it is a direct consequence of sphincter denervation. First, supersensitivity is not found in patients with pupil-sparing third cranial nerve palsies, even those with compressive lesions. Second, the amount of cholinergic supersensitivity is highly correlated with the amount of anisocoria. Finally, loss of supersensitivity occurs with resolution of sphincter palsy.

Several mechanisms have been proposed to explain cholinergic supersensitivity of the iris sphincter in patients with preganglionic third cranial nerve lesions. Jacobson (2)

<table>
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<tr>
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<th>Cholinergic Supersensitivity</th>
<th>Segmental Palsy</th>
<th>Light-Near Dissociation</th>
<th>Tonic Response</th>
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<td>1/1</td>
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<td>NR</td>
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<td>Jacobson (2–4) (31cases)*</td>
<td>11/31</td>
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<td>Coppeto et al (4 cases)</td>
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<td>0/2, 1 NR</td>
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<td>NR</td>
<td>NR</td>
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<td>Ford et al (16) (5 cases)</td>
<td>NR</td>
<td>NR</td>
<td>2/4, NR 1</td>
<td>1/1, NR 4</td>
</tr>
</tbody>
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*Although Jacobson looked at light-near dissociation, he recorded it together with abnormal pupil reactions during ductions, not as a separate finding.

NR, not reported in the paper.
demonstrated in normal subjects that pupils dilated with hydroxyamphetamine would constrict more than untreated pupils in response to dilute pilocarpine (2). Loewenfeld and Newsome (21) also found that in response to pilocarpine, pupils dilated with cocaine constricted more than untreated pupils. It is unlikely, however, that size alone is responsible for cholinergic supersensitivity as in the study of Jacobson (2), the amount of anisocoria was not correlated with net constriction to dilute pilocarpine.

Coppeto et al (12) suggested that cholinergic supersensitivity and a tonic pupillary response in patients with third cranial nerve palsy could result from either transsynaptic degeneration followed by aberrant postganglionic reinervation or from aberrant reinervation of preganglionic fibers to the ciliary ganglion. He considered the concurrence of cholinergic supersensitivity with other classic signs of postganglionic denervation as evidence supporting a transsynaptic mechanism. However, as discussed above, other plausible preganglionic mechanisms may explain these features. In addition, cholinergic supersensitivity occurs too soon after the onset of third cranial nerve palsy in some patients to be explained by transsynaptic degeneration. Slamovits et al (14) and Jacobson (2) observed cholinergic supersensitivity within 5–10 days of the onset of third cranial nerve palsy in some patients. Slamovits et al (14) attributed the rapid-onset supersensitivity to damage to third cranial nerve fibers that do not synapse in the ciliary ganglion. However, there is very little anatomic evidence to support the existence of such a direct pathway.

Several lines of experimental evidence suggest that postganglionic denervation is not required for the development of cholinergic supersensitivity. Supersensitivity or subsensitivity may be produced by any process that alters the state of parasympathetic stimulation of the iris sphincter. Supersensitivity may be produced in experimental animals by continuous exposure to darkness (22,23) or by prolonged treatment with topical cholinergic blockers (24). Subsensitivity may be produced by continuous exposure to light (23) or prolonged treatment with acetylcholinesterase inhibitors (22,25). These studies suggest that the primary determinant of cholinergic sensitivity is the concentration of acetylcholine at the neuromuscular junction, independent of the preganglionic or postganglionic mechanism that regulates the intensity of parasympathetic stimulation.

Another unusual feature of our patient was the etiology of his isolated third nerve palsy, namely an arachnoid cyst. Arachnoid cysts are an uncommon cause of third cranial nerve palsy and comprise approximately 1% of nontraumatic intracranial masses (26). These cysts consist of clear fluid enclosed in reduplicated layers of arachnoid (27). Their MRI signal characteristics are identical to those of cerebrospinal fluid (CSF). These cysts probably originate from maldevelopment of the leptomeninges in the prenatal or early postnatal period (27,28).

By far the most common location for arachnoid cysts is the middle cranial fossa, where they are most often asymptomatic (27). Isolated or nearly isolated cranial neuropathies have been described in association with optic neuropathy (29) and with third (30–33), fourth (34), fifth (35,36), sixth (37,38), seventh (39), eighth (40,41), and tenth (42) cranial neuropathies. Isolated palsies of the third, fourth, and sixth cranial nerves have been reported in association with arachnoid cysts in the middle cranial fossa (37,32), Meckel’s cave (35), quadrigeminal cistern (34), interpeduncular cistern (30), cavernous sinus (31), and suprasellar cistern (29). With the exception of the patient reported by McAvoy et al (38), in whom there was antecedent head trauma and increased intracranial pressure, most cases of cranial nerve palsy due to arachnoid cyst have been slowly progressive.

The number of case reports is too small to permit generalizations about the outcome of ocular motor palsy due to arachnoid cysts. In addition, the cysts are quite heterogeneous in terms of location, size, and chronicity. In the only reported case of an intracavernous arachnoid cyst causing third cranial nerve palsy, no therapy was attempted (31). Of 3 patients with relatively small cysts causing ocular motor palsies, 2 had complete recovery after drainage and excision (35,30), although 1 required reoperation for a recurrence (35). The third patient, who had an acute presentation of a hemorrhagic cyst, was left with a complete third cranial nerve palsy (33). Of 2 patients with ocular motor palsies owing to very large middle fossa cysts, 1 was treated with a cystoperitoneal shunt and had a residual partial sixth cranial nerve palsy that was functionally improved after strabismus surgery (37). A second patient had a cyst fenestration for a large middle fossa cyst producing both visual loss and third cranial nerve palsy (32). Vision was unchanged after cyst fenestration despite a decrease in the size of the cyst. The postoperative status of the third cranial nerve palsy was not mentioned.

In retrospect, several atypical features of our patient’s history and examination might have led to earlier diagnosis of a compressive third cranial nerve palsy. When the ocular motility defect was first noted at age 27 months, he was seen with intermittent exotropia. Although versions were full, the ocular misalignment was inconstant, suggesting a medial rectus palsy. Although the patient’s age and level of cooperation made precise measurements difficult and the misalignment was small, the pupillary abnormality should have suggested a partial third cranial nerve palsy and led to neuroimaging studies and earlier diagnosis. Cholinergic supersensitivity, usually considered typical of postganglionic lesions, should be recognized as also occurring with
preganglionic lesions (2–4). Moreover, our patient lacked the other typical features of postganglionic damage, namely pupillotonia, light-near dissociation, and segmental sphincter palsies. Although these latter features may occasionally be present in preganglionic lesions, their absence is uncommon in postganglionic lesions (1). Postganglionic lesions causing such pupillary abnormalities are distinctly unusual in infants (43,44), and diagnosis should not rest on the finding of cholinergic supersensitivity alone. Given these considerations, one should have a low threshold for obtaining neuroimaging to evaluate for a compressive lesion in children with the ocular motility and pupillary findings we have described in our patient.

REFERENCES

Simultaneous Posterior Ischemic Optic Neuropathy, Cerebral Border Zone Infarction, and Spinal Cord Infarction After Correction of Malignant Hypertension

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Abstract: A 31-year-old woman developed bilateral posterior ischemic optic neuropathy and infarctions of the cerebral arterial border zones and spinal cord after correction of malignant hypertension. Although a few reports have described patients with neurologic abnormalities after treatment of malignant hypertension, full clinical and neuroimaging documentation of this combination of findings has not occurred. This case report suggests that the relative hypotension of autoregulatory failure induced by treatment of malignant hypertension may give rise to these neurologic complications.


Malignant hypertension refers to severe hypertension and organ damage including progressive renal failure, heart failure, and encephalopathy, and requires urgent correction of blood pressure (1–3). A few reports have described patients with neurologic abnormalities after treatment of malignant hypertension (4–9). Nevertheless, simultaneous optic neuropathy, cerebral border zone infarction, and spinal cord infarction have not been fully described previously.

CASE REPORT

A 31-year-old woman presented with a 2-hour history of epigastric pain. She was previously healthy except for taking oral contraceptives for 5 years. On admission, her blood pressure was 270/120 mm Hg. She denied a previous history of systemic hypertension.

Visual acuities were 10/20 in both eyes, and confrontation visual fields were normal. Grade III hypertensive retinopathy was present on ophthalmoscopy.

Hematocrit was 27.1%, and platelet count was 48,000/mm³. The peripheral blood smear showed fragmented and polychromatophilic red blood cells. The serum creatinine level was 1.8 mg/dL, and lactate dehydrogenase was 2,041 U/L.

Malignant hypertension was diagnosed, and she received 20 mg hydralazine intravenously and 10 mg nifedipine sublingually followed by 10 mg fosinopril and 8 mg candesartan orally, which lowered her blood pressure to 120/80 mm Hg within 1 day (Fig. 1). At this time she developed visual blurring in both eyes, which rapidly progressed to complete blindness over several hours. She also complained of bilateral leg weakness, voiding difficulty, and sacral numbness.

Visual acuities were no light perception in both eyes, and the pupils were fully dilated without reaction to light. Ophthalmoscopy showed grade III hypertensive retinopathy with normal optic discs (Fig. 2A).

She could not raise either leg against gravity. Pain and temperature senses were symmetrically reduced over the sacral dermatomes. Deep tendon reflexes were increased, and the Babinski sign was present bilaterally.

T2 brain MRI revealed high signal areas in the medulla bilaterally (Fig. 3), which were hyperintense on diffusion imaging and isointense on apparent diffusion coefficient (ADC) mapping. T2 high signal areas were also found in the superficial border zones between the middle cerebral artery (MCA) and anterior cerebral artery (ACA) territories, which were hyperintense on diffusion imaging and hypointense on ADC mapping (Fig. 3).

Serum aldosterone, renin, epinephrine, and norepinephrine concentrations and urinary excretion of epinephrine, norepinephrine, and vanillylmandelic acid were normal.
MRI and MRA of the kidney to assess an underlying cause for hypertension showed no abnormalities. After maintenance of the blood pressure within the normal range, leg weakness had resolved completely 1 day later. However, 2 months later, visual acuities remained hand movements in both eyes and voiding difficulty had not improved. Bilateral optic disc pallor was now evident (Fig. 2B), and brain MRI showed persistent high signal areas throughout the medulla and spinal cord (Fig. 4).

DISCUSSION
After correction of malignant hypertension, our patient developed bilateral posterior ischemic optic neuropathy, bilateral cerebral border zone infarctions, and extensive spinal infarction with myelopathy. This combination of findings has not been clinically and neuro-radiologically documented before.

There are eight previously reported patients with ischemic optic neuropathy after treatment of malignant hypertension. (4–7) Three of them showed simultaneous optic neuropathy and myelopathy (sphincter disturbance in two and flaccid paraplegia in the remaining one) (4,6). Another 2 patients presented with isolated paraplegia after treatment of malignant hypertension (8,9).

In our patient, clinical and radiologic features support ischemic damage owing to relative hypotension after correction of malignant hypertension as the underlying mechanism of neurologic abnormalities rather than the malignant hypertension itself. The patient did not have neurologic symptoms during the period of high blood pressure, and she had ischemic optic neuropathy rather than retrogeniculate visual pathway infarction, the site of visual loss in patients with visual disturbances from malignant hypertension (posterior reversible encephalopathy syndrome) (10–13). In addition, there was MRI evidence of infarction in the medulla and spinal cord, territories associated with hypotensive rather than hypertensive stroke (10–15).

In 7 of the 8 reported patients with ischemic optic neuropathy after treatment of malignant hypertension, the optic discs were already swollen during the hypertensive crisis. In the eighth patient, initially blurred optic disc margins became more swollen after correction of malignant hypertension, an indication of anterior ischemic optic neuropathy. In our patient, the optic discs were normal when she complained of visual loss and the pupils were unreactive to light, an indication of posterior ischemic optic neuropathy.

The spinal cord, particularly its watershed zone centered at the mid-thoracic level, is a frequent site of ischemic injury (16). However, global ischemia may also affect other levels of the spinal cord, as apparently occurred in our patient. Mild degrees of ischemia may involve the lumbosacral spinal cord (69%), intermediate degrees may affect the lumbosacral and cervical spinal cord in a patchy manner (9%), and severe degrees of ischemia may result in holocord necrosis (17%).

FIG. 1. Time course of our patient's blood pressure, doses of antihypertensive agents, and development of blindness and paraplegia.
Among the reported patients with ischemic optic neuropathy after treatment of malignant hypertension, the visual outcome has been dismal in five, as it was in our patient. One reported patient showed remarkable recovery of vision after prompt restoration of blood pressure with dopamine and norepinephrine, and the remaining 2 patients recovered limited vision after saline infusion, corticosteroids, or stellate ganglion block (7,8). Remarkably, in our patient and in all reported patients, neurologic complications occurred even though blood pressure remained within a conventionally normal level, probably because of a failure of autoregulation. The upper and lower limits of systemic blood pressure between which autoregulation occurs are reset at a higher level in chronic hypertension (18); thus, a sudden lowering of the systemic blood pressure even to normal levels may bring it below the lower limit of autoregulation, in which case cerebral perfusion will fail.

**FIG. 2.** A. Optic fundi 1 day after correction of systemic hypertension show cotton wool spots and normal optic discs. B. Optic fundi 2 months later show bilateral optic disc pallor.

**FIG. 3.** MRI performed 1 day after correction of systemic hypertension. A. T2 axial MRI shows high signal areas in the medulla bilaterally (arrows). B. Diffusion imaging study shows focal high signal (restricted diffusion) areas in the superficial border zone between the middle cerebral artery and anterior cerebral artery territories (arrows).
REFERENCES

Upbeat Nystagmus From a Demyelinating Lesion in the Caudal Pons

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Abstract: A 51-year-old man developed positional vertigo, ataxia, dysgeusia, diplopia, and oscillopsia. Eye movement examination and video-oculographic recording disclosed primary position upbeat nystagmus (PPUN) and a right internuclear ophthalmoplegia. Brain MRI showed a small focal lesion in the right dorsal tegmentum of the caudal pons with signal characteristics consistent with a primary demyelinating central nervous system disease. PPUN has not been described previously with a lesion in such a location. Clinicoanatomic correlation in this patient suggests that a lesion of the superior vestibular nucleus and its efferent crossing ventral tegmental tract could be responsible for the PPUN. This case report contributes to a better understanding of the role of this pathway in humans.

Primary position upbeat nystagmus (PPUN) has been reported in patients with focal brainstem lesions of different locations, usually involving either the rostral pons bilaterally (1-4) or the paramedian dorsal part of the caudal medulla (1,5-13). The pathophysiology of the caudal medullary lesions is not clear (14).

We report a patient in whom PPUN was due to a small unilateral lesion in the dorsal tegmentum in the caudal pons, a location not previously reported for PPUN. This case report highlights the brainstem pathways involved in vertical vestibular eye movements in humans.

CASE REPORT

A 51-year-old man without a prior medical history experienced the subacute onset of vertigo, ataxia, dysgeusia, vertical diplopia, and oscillopsia. Examination disclosed that his walking was moderately ataxic. He showed a slight right lower motor neuron facial weakness and reduced taste on the right anterior two thirds of the tongue. Neuro-ophthalmologic examination revealed findings consistent with a left skew deviation (right hypertropia), a mild right internuclear ophthalmoplegia (INO) manifested by decreased velocity of the adducting right eye during left ward saccades, and PPUN. Results of cardiovascular and general physical examinations were normal.

T2 MRI showed a single area of high signal in the brainstem in the right caudal part of the pontine tegmentum, extending longitudinally 7 mm from the caudal pons just above (maximum 3 mm) the sixth nucleus and terminating just before the mid-pons (Fig. 1). The lesion extended laterally 7 mm from midline to the trigeminal nuclei. There were two other high signal areas around the lateral ventricles. The lesions were hypointense on T1 MRI and did not enhance. Lumbar puncture showed a normal cell count, a protein level of 0.53 g/L, and oligoclonal bands. Results of serology tests for lyme disease, HIV, and syphilis were negative.

A first manifestation of multiple sclerosis was diagnosed, and the patient was given methyl prednisolone (1 g/day for 3 days) intravenously. One month later, the patient had no more complaints, and results of clinical examination were normal. Fluid-attenuated inversion recovery image (FLAIR) MRI performed at that time showed a persisting hypersignal of the right posterior part of the caudal pontine tegmentum without any new lesions.

Eye movements were recorded using infrared video-oculography (200 Hz frequency; Visuo200; Synapsys, Marseille, France). Nystagmus was upbeat in the primary position of gaze, with mean amplitude of 10° and a mean velocity of 7°/sec (Fig. 2). The nystagmus slow phase was linear in the primary position of gaze. Nystagmus velocity was increased in upgaze (12°/sec) with an exponentially decreasing velocity waveform. In right gaze, the velocity also increased (10°/sec), and the...
nystagmus showed a torsional clockwise (from the patient’s viewpoint) component. In left gaze, from about 20° eccentricity, the nystagmus changed to left-beating. The velocity of the upbeat nystagmus decreased in downgaze and during convergence. The relationship of the nystagmus to head position was not tested.

Horizontal pursuit (amplitude: 34°, frequency: 0.15 Hz) was smooth except for beats of left-beating nystagmus in left gaze. Vertical upward pursuit (amplitude: 24°, frequency: 015 Hz) was interrupted by catch-up saccades or quick phases; downward pursuit was normal. The vestibulo-ocular reflex was not recorded.

Saccades were tested in the direction of 15 and 30° to the right and left and in the direction of 10° up and down. Saccades were of normal gain except for the leftward eye movement made by the right eye. In this case, eye movement recording showed saccades of decreased gain (mean accuracy 76%) with appropriate velocity (mean peak velocity 257°/s) compared with the left eye (accuracy: 97%; velocity: 312°/s), consistent with a mild right INO.

**DISCUSSION**

Vertical nystagmus in the primary position of gaze is thought to be the consequence of asymmetries in the cerebello-brainstem network involved either in the vertical “neural integrator” or the vestibulo-ocular reflex (14,17). Pursuit disorders are also usually associated, particularly in the direction of the vertical quick phase, but such abnormalities could be the consequence rather than the cause of most of the jerk nystagmus.

The human brainstem pathways involved in vertical vestibular eye movements are not yet well known, and previously reported cases of PPUN owing to brainstem damage are relatively rare and involve the caudal medulla or less frequently the central part of the mid-pons and rostral pons (1-13) but not so far the lateral part of caudal pons as reported here.

Damage to one of the three excitatory vestibulo-oculomotor tracts involved in upward eye movements (17) could theoretically account for the pathophysiology of PPUN. The first excitatory tract originates in the medial vestibular nucleus (MVN), decussates at this level, and runs in the contralateral medial longitudinal fasciculus (MLF) before connecting with the third cranial nerve nuclei (17). The second excitatory tract is the crossing ventral tectal tract (CVTT), described only in the cat (16) but probably also existing in humans, as suggested 20 years ago (18). The CVTT originates in the superior vestibular nucleus.
(SVN), first courses rostrally in the paramedian posterior tegmentum of the caudal pons, and then arches ventrally and medially at the mid-pons level and decussates just above this level in the ventral tegmentum or the dorsal part of the basis pontis (4) before reaching the third cranial nerve nuclei via the ventral tegmentum of the rostral pons and caudal midbrain (Fig. 1C). The third excitatory tract could be within the brachium conjunctivum (BC), also known as the superior cerebellar peduncle, receiving afferent input from the SVN region, coursing rostrally in the caudal tegmentum, and decussating in the caudal midbrain before projecting to the third cranial nerve nuclei.

In our patient, the lesion was in the vicinity of these three tracts, either in the caudal pons (Fig. 1A) or in the mid-pons (Fig. 1B).

First, the lesion probably damaged the right MLF because a slight right INO and left skew deviation existed in our patient (15,19). The lesion appeared to involve this fascicle at the caudal pontine level (Fig. 1A). However, we believe that MLF damage was not mainly responsible the PPUN here, given that the impairment was unilateral and the INO was moderate and the previously reported cases of unilateral INO, even those with adduction saccade paralysis, were not associated with a PPUN and at most

**FIG. 2.** Plot of vertical eye position (in degrees) versus time, in upgaze, primary eye position, and downgaze. The slow phase of the vertical nystagmus was linear in the primary position of gaze. The velocity of nystagmus was increased in upgaze with an exponentially decreasing velocity waveform and was slightly decreased in downgaze.
vestibular eye movements is relatively balanced (20). In our patient, only the decelerating slow phase as seen in upgaze might reflect a lesion of the MLF. Absence of PPUN with an MLF lesion is probably due to the fact that impairment affecting the excitatory tracts involved in upward and downward vestibular eye movements is relatively balanced (20).

Second, even though the lesion was located very close to the BC, this tract appeared to be spared here. However, the role of the BC in upward vestibular eye movements is currently uncertain. Although a few cases of PPUN have previously been attributed to possible BC damage (21–23), such cases are not convincing because lesions were hemorrhagic or tumorous, very large, and bilateral in the brainstem. Another fascicle in the caudal tegmentum that may be involved is the putative CVTT, which is very close to the BC in the caudal pons. Furthermore, the only reported patients with small lesions that were restricted to the BC and located more dorsally compared with the lesion in our patient had isolated positional downbeat nystagmus, not PPUN (24).

Third, experimental data on the role of the BC in the upward vestibulo-ocular reflex seem to be much less documented than those concerning the other two tracts (MLF and CVTT) (17). Therefore, we believe that the PPUN of our patient was not due to extension, which was not visible by imaging, of the lesion to the BC. Finally, the PPUN in our patient could perhaps have resulted from a SVN-CVTT impairment. Indeed, the upper pole of the SVN was clearly damaged by the lesion and the CVTT is supposed to leave this nucleus rostrally in the posterior tegmentum of the caudal pons, also damaged here (Fig. 1C). The right peripheral facial paresis observed in our patient probably resulted from such caudal pontine damage. More rostrally, at the mid-ppons level, the CVTT is supposed to be located in the ventral tegmentum (16), apparently spared in our patient (Fig. 1B).

Thus, a lesion of the SVN-CVTT pathway in the caudal pons appears to be principally responsible for the PPUN of our patient. This case report emphasizes for the first time in humans the critical role of damage to the origin of this pathway in the genesis of upbeat nystagmus. The clearly unilateral feature of brainstem damage could also explain the asymmetrical torsional component of nystagmus in lateral gaze (17). It should be noted that the slow phase of this upbeat nystagmus was linear in the primary position of gaze, suggesting vestibular imbalance (17), and decelerating in upgaze, consistent with integrator failure (17). These two aspects of the upbeat nystagmus slow phase, which have previously been observed in patients with either pontine or medullary lesions (14) and even in the same patient (4), may coexist as the vestibular system and its circuitry could contribute to eye movement integration (17). Lastly, unilateral dorsal tegmental damage may account for the ipsilateral dysgeusia observed in our patient, considering that a medullothalamic tract involved in taste runs through this region (25). Further studies are required to determine the specific roles of the MVN-MLF and SVN-CVTT pathways in the transmission of upward vestibular eye movement signals.

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Atypical Teratoid/Rhabdoid Tumor Arising From the Third Cranial Nerve

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Abstract: An otherwise healthy 6-week-old girl who presented with an isolated left third cranial nerve palsy underwent MRI that revealed an enhancing mass intrinsic to the left third cranial nerve. Rapid enlargement of the lesion over 1 month led to subtotal neurosurgical resection of an atypical teratoid/rhabdoid tumor (AT/RT), a rare, highly aggressive malignancy of infancy closely related histologically to medulloblastoma and primitive neuroectodermal tumor. Despite aggressive chemotherapy, the patient died within 6 months of presentation. This is the first report of an AT/RT presenting as an isolated third cranial nerve palsy caused by tumor arising from within the nerve.


A typical teratoid/rhabdoid tumor (AT/RT) is a rare, highly aggressive, central nervous system (CNS) malignancy of infancy that was definitively distinguished from its closest histologic relatives, medulloblastoma and primitive neuroectodermal tumor (PNET), in a 32-patient case series in 1995 (1). Since then, approximately 200 cases have been reported, 94% of which have been seen in patients younger than 5 years (2). Symptoms of AT/RT are either nonspecific, including lethargy, vomiting, or failure to thrive, or related to the location of the tumor, including cranial nerve palsies, ataxia, head tilt, or extremity paresis (3). We report an infant presenting with an isolated third cranial nerve palsy caused by AT/RT intrinsic to the third cranial nerve, a previously undescribed phenomenon.

CASE REPORT

An otherwise healthy 6-week-old girl was seen with 3 days of left eye outward deviation. The patient was the product of an unremarkable pregnancy and was delivered without complications by cesarean section, weighing 9 pounds 8 ounces, at full term. The patient had no history of illness, travel, or trauma. There was no pertinent family history.

Examination revealed that each eye was capable of fixing and following intermittently with equal aversion to occlusion. In primary gaze, the right eye was centered with normal eyelid position, and the left eye was exotropic and hypotropic with ptosis (Fig. 1A). Ocular ductions of the right eye were full. The left eye displayed reduced supraduction (Fig. 1B) and adduction (Fig. 1C). There was variable upper lid ptosis. A review of photographs of the patient taken during the first 4 weeks of life revealed that these ophthalmic abnormalities were not present at that time. The right pupil measured 4 mm in dark and 2 mm in light, the left pupil measured 6 mm in dark and 4 mm in light. There was no afferent pupillary defect. Anterior segment and dilated ophthalmoscopic examinations were normal in both eyes.

Brain MRI revealed an 8-mm homogenously enhancing mass within the interpeduncular cistern inseparable from the left third cranial nerve (Fig. 2A,B). Results of CT angiography, MRA, and lumbar puncture with cytology and flow cytometry were unremarkable. Results of complete blood count, basic chemistry panel, C-reactive protein, erythrocyte sedimentation rate, liver function tests, thyroid function tests, and Coombs test were normal. Repeat MRI of the brain and spine after 1 month revealed a significant increase in the size of the mass to 18 mm with extension along the left third cranial nerve and invasion of the midbrain and pons (Fig. 1C). There was no evidence of leptomeningeal dissemination.

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A left frontotemporal craniotomy with orbitozygomatic extension disclosed that the left third cranial nerve appeared normal anteriorly but was expanded by tumor posteriorly (Fig. 3A). With no clear boundary between tumor and brainstem parenchyma, a subtotal resection was performed.

Light microscopy revealed hemorrhage, necrosis, mitotic figures, and large pink, anaplastic cells with vesicular nuclei and prominent nucleoli with cytoplasmic inclusions, cells characteristic of rhabdoid tumors (Fig. 3B–C). Immunohistochemistry demonstrated tumor cells to be positive for epithelial membrane antigen (EMA) (Fig. 3E), smooth muscle actin (SMA) (Fig. 3F), and glial fibrillary acidic protein (GFAP) and negative for desmin, synaptophysin, and human melanoma black-45 (HMB-45). There was loss of nuclear expression of integrase interactor-1 (INI1) within tumor

**FIG. 1.** External photographs of the infant showing features of a left third cranial nerve palsy. A. Primary gaze position: right eye centered and left upper lid ptosis. B. Partial upgaze: reduced elevation of the left eye. C. Partial right gaze: reduced abduction of the left eye.

**FIG. 2.** Magnetic resonance images of the infant with an atypical teratoid/rhabdoid tumor. A, B. Postcontrast T1 axial and sagittal MRIs at presentation shows a 6 x 8 x 8 mm mass with homogenous enhancement within the interpeduncular cistern inseparable from the left third cranial nerve. C. Postcontrast T1 sagittal MRI performed 1 month later shows an increase in the size of the mass to 22 x 18 x 18 mm with extension along the third cranial nerve and invasion of the midbrain and pons.
FIG. 3. A. Intraoperative photograph: superior view of the anterior brainstem. The third cranial nerve (arrow) is lateral to the internal carotid artery, and the optic nerve (triangle) is located medially. A white, gelatinous tumor (star) is seen arising from the posterior aspect of the third cranial nerve. B–F. Histopathology of the surgical specimen. B. Small and large blue cells arranged in cords and nodules separated by fibrous septae with hemorrhage, necrosis, and mitotic figures (hematoxylin and eosin; original magnification x40). C. Anaplastic, large pink cells with cytoplasmic inclusions and vesicular nuclei with prominent nucleoli (hematoxylin and eosin; original magnification: x400). D. Large tumor cells exhibit no nuclear labeling for integrase interactor-1 (INI1), whereas infiltrating lymphocytes and endothelial cells show the expected nuclear reactivity of normal cell types (BAF47 anti-IN1 immunohistochemical staining; original magnification x400) (4). E. Tumor cells exhibit positive labeling for epithelial membrane antigen (EMA) (anti-EMA immunohistochemical staining; original magnification: x400). F. Tumor cells exhibit positive labeling for smooth muscle actin (SMA) (anti-SMA immunohistochemical staining; original magnification x400).
cells, supporting a diagnosis of AT/RT (Fig. 3D). Analysis of DNA isolated from formalin-fixed tissue did not reveal a coding sequence mutation in the INI1 gene.

A five-cycle chemotherapeutic regimen was started according to the Head Start II Protocol, including vincristine, etoposide, cyclophosphamide, methotrexate, and cisplatinum, with the eventual goal of hematopoietic stem cell transplantation. Five months after the initial presentation, the patient developed vomiting. Repeat MRI revealed hydrocephalus with widespread leptomeningeal disease extending around the brainstem and spine. A palliative ventriculoperitoneal shunt was placed. The patient died several weeks later, 6 months after the initial presentation.

DISCUSSION

Among acquired, pupil-involving third cranial nerve palsies in a child, 10% are due to neoplasm (5,6). Although the sixth and seventh cranial nerves are most commonly involved with AT/RT (3), the current patient demonstrates that AT/RT may occur intrinsic to the third cranial nerve and present as an isolated third cranial nerve palsy.

AT/RTs represent approximately 1.3% of pediatric brain tumors (2). MRI typically reveals isointense or hypointense signal on both T1 and T2 sequences and enhancement with gadolinium. The signal is heterogeneous due to cysts, calcification, hemorrhage, and necrosis (7). However, there are no specific imaging features for AT/RTs. PNETs have similar imaging characteristics. Compared with PNETs, AT/RTs may have an increased rate of leptomeningeal metastasis at presentation and may be more likely to have associated hemorrhage (7). Both types of tumors require assessment of cerebrospinal fluid cytology and MRI scanning of the entire neuroaxis to rule out subarachnoid dissemination.

Definitive diagnosis of AT/RT is made by correlating histologic and immunohistochemical findings, as in the present patient. Histologically, rhabdoid cells can vary in size from small to large. The larger forms typically have homogeneous bright pink cytoplasm that may appear to contain an inclusion. Cell margins are usually well-defined and nuclei are round, often with a prominent nucleolus (1). The immunohistochemical profile of these tumors is complex, as there is often variation of expression within a given tumor, but it is essential to distinguish them from other primary nervous system tumors, most commonly germ cell tumors and PNETs (3). Rhabdoid cells are most commonly positive for EMA, vimentin, and SMA. They may also express GFAP, neurofilament protein, keratin, and synaptophysin. In contrast, they are consistently negative for desmin, which is confined to mesenchymal tumors and PNETs. Similarly, germ cell markers, such as placental alkaline phosphatase and α-fetoprotein, are consistently negative in rhabdoid tumor cells (1,3,8,9). HMB-45, a marker for melanocytic tumors, is also negative.

Supplementing these immunohistochemical characteristics, the absence of nuclear expression of INI1 has emerged as a critical tool for accurate AT/RT diagnosis (10). The INI1 protein is a component of the chromatin-remodeling complex SW1/SNF/BAF that functions in the transcriptional activation and repression of a variety of genes. Although its precise role in tumorigenesis is not defined, INI1 is the predominant rhabdoid tumor suppressor gene. Mutation or deletion of both copies of the INI1 gene is observed in approximately 70% of rhabdoid tumors, with an additional 20%–25% having reduced expression at the RNA or protein level. In addition, approximately 18% of patients with nervous system AT/RTs have germline mutations (4). As all normal cells at all stages of development exhibit nuclear INI1 expression, blood vessels, fibroblasts, and infiltrating lymphocytes serve as internal positive controls for INI1 immunohistochemistry, as in the present patient. Although loss of nuclear expression of INI1 is believed to be highly specific for AT/RT and retention of nuclear expression of INI1 strongly suggests an alternate diagnosis, loss of INI1 staining has been reported rarely in other tumors (4,10).

Compared with an 85% 5-year survival for standard-risk pediatric medulloblastoma, the prognosis of AT/RT is poor, with death occurring in 85% of patients within 2 years (4,11). Therefore, correct diagnosis using histologic evaluation and immunohistochemistry is important to allow appropriate prognostication and treatment.

This patient demonstrates that AT/RT may present as an isolated third cranial nerve palsy and highlights the importance of neuroimaging in instances of acquired cranial nerve palsy in children, as well as the histologic and genetic features that differentiate AT/RT from other primary nervous system malignancies of infancy.

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Reversible Chest Tube Horner Syndrome

Michael Levy, MD, PhD and David Newman-Toker, MD, PhD

Abstract: A 54-year-old woman who underwent chest tube placement after a lung biopsy was found on the first postoperative day to have ipsilateral ptosis and miosis, suggesting a Horner syndrome. A chest CT scan showed that the tip of the chest tube was apposed to the stellate ganglion. Repositioning of the chest tube later on the first postoperative day led to complete reversal of the Horner syndrome within 24 hours. We propose that the Horner syndrome arose as a result of pressure on the stellate ganglion, which interrupted neural conduction but did not sever the sympathetic pathway (“neurapraxia”). Whether prompt repositioning of the chest tube was critical in reversing the Horner syndrome is uncertain.

(A) 54-year-old woman was noted to have asymmetric pupils after a left upper lung wedge resection for diagnostic biopsy of a lung mass that was followed by routine

FIG. 1. A. Line drawing illustrating the normal three-dimensional anatomy of the posterior thorax and stellate ganglion from an oblique, anterolateral vantage point. (Drawn by Timothy H. Phelps, MS, Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine.) Postcontrast sagittal (B), coronal (C), and axial (D) chest CTs of our patient show the position of the chest tube in relation to nearby structures, including the stellate ganglion. FR, first rib; SA, subclavian artery; VA, vertebral artery; VB, vertebral body.

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placement of a thoracostomy tube. Our bedside examination on the first postoperative day confirmed left upper lid ptosis and left miosis. There were no deficits of ocular motility or obvious asymmetry of facial sweating. A left Horner syndrome was diagnosed and a chest CT with contrast was recommended to determine the precise etiology.

As seen on the CT image, the chest tube was in direct apposition to the stellate ganglion posterior to the subclavian artery (Fig. 1). Although the stellate (cervicothoracic) ganglion can only be visualized surgically or by MRI (1), its regional location can be confidently assigned using three-dimensional CT reconstructions of the upper chest. Repositioning of the chest tube later on that first postoperative day led to complete reversal of the Horner syndrome within 24 hours, with no residual ptosis, miosis, or pupillary dilatation lag.

The incidence of Horner syndrome after chest tube placement is less than 1% (2), but chest tubes account for nearly half of all cases of iatrogenic Horner syndrome in patients undergoing thoracic surgical procedures (2). As expected, most cases associated with tube placement are noted within 12–72 hours of the procedure (2,3), but others have been reported to occur up to 2 weeks later (3). Urgent repositioning of chest tubes is associated with rapid reversal of or gradual recovery from Horner syndrome in the majority of reported cases (2,4,5).

The presumed mechanism of injury in such early-onset and rapidly reversible cases is compressive neurapraxia, or interruption of neural conduction without structural damage to the pathway (4). Only a thin layer of endothoracic fascia separates the apical lung pleura from the stellate ganglion (6), and direct pressure from the tube tip is believed to be responsible for the Horner syndrome. However, cases of Horner syndrome with apparently delayed onset are not infrequent and require some explanation beyond direct compression alone. Although some delays in diagnosis may simply reflect the clinical subtlety of the sign rather than the underlying pathogenesis, truly delayed onset can sometimes result from chest tube migration, such as when the patient is mobilized from bed (5). Whether tube migration accounts for most cases with delayed onset is unclear. Other explanations to account for delayed symptoms have been proposed, including inflammation, fibrosis, and local hematoma formation (3). Whether these mechanisms might also help explain cases of patients with incomplete recovery, or rare cases occurring after removal of the tube (3) remains speculative.

Routine chest radiography does not permit direct visualization of the anatomic relationship between a chest tube and sympathetic chain or stellate ganglion. However, in the appropriate clinical context, an apical and medial location of the chest tube tip is highly suggestive of a “chest tube Horner syndrome” (3,5). A chest CT with contrast offers the possibility of high-resolution anatomic lesion localization, as well as the opportunity to diagnose dangerous alternative causes not uniformly identified on chest radiographs such as vascular dissection or pseudoaneurysm formation.

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REFERENCES

Neurosarcoidosis Mimicking a Malignant Optic Glioma

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Abstract: A 55-year-old African-American man developed progressive unilateral optic neuropathy and periocular pain. MRI showed thickening and enhancement of the mid-orbital segment of the ipsilateral optic nerve. Optic neuritis was diagnosed, and he was treated with corticosteroids without improvement. After being lost to follow-up, he returned with worsening vision in the affected eye, aggravated pain, and proptosis. MRI now showed thickening and enhancement of the entire orbital and intracranial segments of the optic nerve. Because the patient had no light perception in that eye and a malignant glioma was suspected, he underwent optic nerve biopsy that revealed non-caseating granulomas throughout the optic nerve tissue. CT body imaging failed to disclose other evidence of sarcoidosis. Neurosarcoidosis limited to the optic nerve is rare but should always be suspected in such circumstances. An exhaustive effort to find extracranial evidence for this diagnosis should be undertaken before resorting to optic nerve biopsy.

A 25-year-old African-American man presented to the neurology clinic with progressive left eye vision loss, proptosis, and periocular pain.

“Atypical optic neuritis” had been diagnosed 9 months previously. MRI at that time had shown enhancement in the mid-portion of the left optic nerve (Fig. 1A). He had been treated with 1 g of intravenous prednisolone for 4 days, followed by oral prednisone in a tapering dose for 14 days with slight symptomatic improvement. Against medical advice, the patient did not return to the clinic for follow-up examinations.

The patient finally returned 9 months later because left eye visual loss had recurred, together with left periocular pain and proptosis progressing over several months. The patient had no light perception in the left eye. The left globe was mildly proptotic (3 mm) without lid retraction and was deviated laterally. There was a left afferent pupillary defect. Ophthalmoscopy revealed mild left optic nerve pallor. Results of the remainder of the ophthalmic examination were unremarkable.

MRI now showed diffuse enlargement and enhancement of the left optic nerve extending from the globe to the optic chiasm (Fig. 1B). Coronal sections revealed that the signal abnormalities affected the meninges and parenchyma of the optic nerve (Fig. 2).

The patient had a radiograph of the chest and CT of the chest, abdomen, and pelvis, which showed no radiographic manifestations of sarcoidosis. Because of concern for a neoplastic process such as a malignant glioma, the left
optic nerve was biopsied. At the time of biopsy, the visual appearance and frozen section suggested glioma. But the final histologic examination revealed non-caseating granulomas with giant cells completely replacing the meninges and normal architecture of the nerve, a pattern consistent with sarcoidosis. The patient was treated with corticosteroids without improvement in his vision.

Sarcoidosis involves the meninges, brain, spinal cord, or nerves (neurosarcoidosis) in fewer than 5% of patients (1). Neurosarcoidosis most commonly presents with cranial nerve palsies, usually those of the facial and optic nerves (2). Optic nerve sarcoidosis may present as isolated involvement of the nerve, optic chiasm, or optic nerve sheath. Most cases show mixed involvement (3). Tabulation of case reports and case series yielded 134 patients with intracranial sarcoidosis confirmed by MRI or CT. Lesions were seen in the optic nerve in 26.8% (n = 36), in the optic chiasm in 16.4% (n = 22), and in the optic nerve sheath in 5.8% (n = 8) of patients (3–16). Lesions of the nerve sheath have a better prognosis and can mimic a meningo, idiopathic orbital inflammation (orbital pseudotumor), or leptomeningeal spread of tumor, whereas lesions of the optic nerve can mimic optic neuritis or an optic glioma (9). Regardless of location in relation to the optic nerve, sarcoidosis in these reports presented with progressive vision loss (3).

A patient presenting with isolated optic nerve sarcoidosis without additional lesions is very unusual (3,17). Over the last 40 years, 20 patients with isolated biopsy-proven optic nerve sarcoidosis have been described (7,9,11). The majority of these reports predated the availability of MRI. Preoperative suspicion of an optic nerve meningioma or glioma was based on optic canal enlargement on plain radiography (11). How many of these patients may have had additional intracranial lesions is not known.

Most low-grade optic gliomas present in children. The differential diagnosis for optic nerve enhancement in the adult includes optic neuritis, sarcoidosis, and optic glioma (18). The adult form of optic nerve glioma is highly aggressive, very rare, and usually fatal within 1 year (19).

Several authors have advocated a trial of corticosteroids before biopsy of the optic nerve, given that most meningiomas or gliomas will not show clinical or radiologic improvement, whereas neurosarcoidosis typically will show improvement (3).

An adult patient presenting with optic pathway symptoms, isolated optic nerve enhancement, and features atypical for demyelinating optic neuritis will be a diagnostic challenge that can be frequently resolved by short-term follow-up examinations and a careful clinical history. Sarcoidosis should be remembered because of its ability to mimic multiple imaging findings. A systemic imaging evaluation for characteristic lesions or a successful trial of corticosteroids may suggest this diagnosis and obviate the need for optic nerve biopsy.

REFERENCES

Bimedial Rectus Hypermetabolism in Convergence Spasm As Observed on Positron Emission Tomography

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FIG. 1. A, The patient has a left head tilt and esotropia in primary gaze position. The right eye is slightly hypertropic, probably due to skew deviation. B, 18F-fluorodeoxyglucose postion emission tomography (PET) in the axial (left) and coronal (right) planes shows markedly increased metabolism in the medial rectus muscles (arrows). C, For comparison, a normal subject looking straight ahead shows normal PET metabolism in the rectus muscles (arrows). Color bar on right indicates the increasing degrees of metabolism in ascending order.
Abstract: A 52-year-old man developed vertical gaze palsy, convergence spasm, and convergence-retraction nystagmus due to glioblastoma of the right thalamus. 18F-fluorodeoxyglucose positron emission tomography (PET) inadvertently demonstrated markedly increased metabolism in the medial rectus muscles. The hypermetabolism indicates active contraction of these extraocular muscles due to excessive convergence drive attributed to inappropriate activation or disrupted inhibition of convergence neurons by the diencephalic lesion.


A 52-year-old man presented with a 5-day history of headache, diplopia, and memory loss. He showed leftward head tilt, esotropia, right hypertropia, bilaterally impaired abduction, and upgaze palsy. Vertical saccades and convergence induced convergence-retraction nystagmus (Fig. 1). Pupillary responses were decreased bilaterally without light-near dissociation. These findings were consistent with a dorsal midbrain (pretectal) syndrome (1,2).

18F-fluorodeoxyglucose positron emission tomography (PET) showed increased metabolism in the mass lesion and in the medial rectus muscles (Fig. 1). MRI disclosed a mass lesion in the right thalamus with ventriculomegaly (Fig. 2). Stereotactic biopsy of the tumor revealed glioblastoma.

PET-detected hypermetabolism of the extraocular muscles has been observed during self-generated versional eye movements in the dark (3). During vergence eye movements, PET activation has been documented in the tempororo-occipital junction, the inferior parietal lobule, and right fusiform gyrus bilaterally (4). However, there are no PET data on the metabolic changes of the extraocular muscles during vergence. The findings in our patient indicate active contraction of the medial recti during convergence spasm. As we did not detect hypermetabolism in the cortical areas responsible for vergence eye movements in our patient, disruption of descending inhibition on the convergence neurons or irritation of the convergence neurons due to the diencephalic lesion may have generated an excessive convergence drive (5).

REFERENCES
Loss of Myelinated Retinal Nerve Fibers From Chronic Papilledema

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FIG. 1. A. On the first postoperative day after resection of a suprasellar mass there is chronic optic disc edema (papilledema) of both optic discs and myelinated nerve fibers in the left eye. B. Two months postoperatively, both optic discs have become pale and the myelinated nerve fibers appear thinner. C. Thirty months postoperatively, the optic discs are still pale, and the myelinated nerve fibers have disappeared along with development of atrophy of the nerve fiber layer.

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Abstract: An intracranial pilocytic astrocytoma was diagnosed in a 13-year-old boy after he presented with headaches and visual disturbances. The initial ophthalmoscopic examination revealed papilledema bilaterally and myelinated retinal nerve fibers (MRNFs) in the left eye. Serial ophthalmoscopic examinations demonstrated gradual fading of the MRNFs beginning 2 months after tumor resection and their complete disappearance by 2 years after surgery. The disappearance of MRNFs has been described in the presence of ischemia, compression, glaucoma, and demyelinating disease of the optic nerve. This patient demonstrates that loss of myelinated nerves fibers may also occur with the optic atrophy that may follow chronic papilledema.


A 13-year-old boy presented with a 3-day history of headache, nausea, and visual disturbance. MRI revealed a heterogeneous suprasellar mass originating from the anterior hypothalamus and massive hydrocephalus. A craniotomy with subtotal excision was performed, and the mass was confirmed to be a juvenile pilocytic astrocytoma. On the first postoperative day, visual acuity was 20/100 in the right eye and 20/400 in the left eye. He could not identify any of the Ishihara pseudochromatic plates. The pupils were sluggishly reactive to light with a subtle left relative afferent pupillary defect. Goldmann perimetry revealed severely constricted visual fields with 5 central islands in both eyes. Indirect ophthalmoscopy revealed bilateral optic edema with mild pallor. Extensive myelinated retinal nerve fibers (MRNFs) continuous with the optic disc were present in the patient’s left eye (Fig. 1A).

On reexamination 2 months after surgery, visual acuity was hand motions in both eyes. Ophthalmoscopy revealed optic nerve pallor in both eyes. The myelination of the retinal nerve fibers in the left eye had become less dense with enhanced visibility of the retinal vasculature (Fig. 1B).

On reexamination 30 months after surgery, visual acuity had improved to 20/400 in the right eye and 20/200 in the left eye. Ophthalmoscopy now showed complete disappearance of the MRNFs and entire visibility of the previously obscured retinal vasculature (Fig. 1C).

MRNFs are usually an asymptomatic developmental anomaly and most often are detected incidentally on routine examination. They appear ophthalmoscopically as gray-white striations with frayed margins that follow the distribution of an underlying wedge of axons (1). These pathologic and anatomic features of MRNFs were first elucidated by Virchow in 1856 (1).

The normal retina is devoid of oligodendrocytes and its constituent bundles of lipoprotein lamellae known as myelin (1,2). The presence of MRNFs therefore highlights an anomaly in the development of the anterior visual pathway. In the normal course of development, myelination of the pregeniculate pathway commences in the lateral geniculate body at 5 months of gestation, tracking anteriorly to terminate at the lamina cribrosa around the time of birth (3). In some individuals, myelination may extend anterior to the lamina cribrosa to involve the optic nerve head or retina.

In studying 3968 consecutive autopsy cases, Straatsma et al (1) determined the prevalence of MRNFs to be 0.98%. Histologic examination has shown that the underlying retina in MRNFs usually does not exhibit any pigmented, vascular, or associated morphologic abnormalities, although microcystoid degeneration of the nerve fiber layer has been noted. Although usually presenting as congenital and stationary lesions, MRNFs have been rarely described as being acquired or progressive (4). They can be associated with many other ocular and systemic abnormalities, including neurofibromatosis, keratoconus, coloboma, polycoria, and craniofacial dysostosis (5).

Despite the existence of multiple theories, the exact pathogenesis of MRNFs remains to be elucidated. Based on the observation that animals with a poorly developed lamina cribrosa have frequent myelination of the retina, one proposal is that there may be a physical defect in the lamina itself (5). Another postulate is that oligodendrocytes are anomalously located in the retina, resulting in aberrant myelination (1). Recent results in experimental neurobiology, however, suggest that soluble proteins in the retina play an integral role in both the migration and differentiation of oligodendrocyte precursors (2). Thus, myelination may be the result of a failure in an inhibitory chemical signal rather than a physical defect in the lamina itself.

Optic atrophy due to trauma, ischemia, compression, or inflammation can result in loss of ganglion cell axons and their respective myelin sheaths (3). Loss of MRNFs has been reported in association with anterior ischemic optic neuropathy, syphilis, pituitary tumor, glaucoma, central retinal artery occlusion, plaque radiotherapy, Leber hereditary optic neuropathy, and pars plana vitrectomy (1,3,6,7). The mechanism common to the loss of myelin in the above cases is neuronolytic degeneration, in which myelin breakdown is due to atrophy of ganglion cell axons. Loss of retinal myelin has also been shown in the presence of demyelinating inflammatory optic neuritis, for which periaxial degeneration remains the probable mechanism, with demyelination being the primary event and axonal loss following secondarily (3).

Although atrophy and loss of the retinal nerve fibers is often a subtle ophthalmoscopic finding, our patient dramatically highlights the extent of nerve fiber layer damage by
demonstrating complete disappearance of extensive intraocular myelin. It is well recognized that secondary optic atrophy can ensue after chronic papilledema. In our patient, the loss of myelination is postulated to occur via neuronolytic degeneration consequent to atrophy of ganglion cell axons from a sustained increase in intracranial pressure. To the best of our knowledge, this is the first patient in whom loss of MRNFs due to chronic papilledema has been photographically documented.

REFERENCES
Radiation Therapy for Visual Pathway Tumors

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Abstract: The multimodality management of visual pathway tumors frequently involves radiation. Most commonly, photons are delivered via multiple focused beams aimed at the tumor while sparing adjacent tissues. The dose can be delivered in multiple treatments (radiation therapy) or in a single treatment (radiosurgery). Children with visual pathway gliomas should be treated with chemotherapy alone, delaying the use of radiation therapy until progression. Definitive radiation therapy of optic nerve sheath meningiomas results in stable vision in most patients. Radiation therapy or radiosurgery for pituitary tumors can result in control of both tumor growth and hormone hypersecretion. Postoperative radiation therapy or radiosurgery of craniopharyngiomas significantly improves local control rates compared with surgery alone. Radiation therapy is highly effective for eradicating orbital pseudolymphoma and lymphoma. The risk of complications from radiation treatment is dependent on the organ at risk, the cumulative dose it receives, and the dose delivered per fraction.

(Ionizing radiation is a mainstay of the treatment of intracranial lesions. Practitioners of this art have at their command an arsenal of varying tools, all of which serve one purpose: to deliver a specific dose of radiation to a specific target with a specific intent and the lowest possible dose to normal tissues.

THE TOOLS

Radiation therapy (RT) most commonly uses photon energy generated by linear accelerators or cobalt-60 sources. Photons are delivered as focused beams aimed at the tumor from varying angles. RT can be delivered in multiple treatments or in a single treatment. “Three-dimensional conformal” RT (3DCRT) conforms the volumetric distribution of the desired dose to the shape of the target. The basic rationale for using conformal delivery is to spare adjacent normal tissue from receiving unnecessary radiation. “Intensity-modulated” RT (IMRT) is a specialized subset of 3DCRT resulting in a non-uniform dose distribution. Stereotactic targeting is used when a very high degree of accuracy and precision is required. “Image-guided” RT (IGRT) uses real-time imaging to confirm that the target is localized correctly with respect to the radiation beams.

Photons, Electrons, and Protons

The three most common types of radiation used in the treatment of tumors are photons, electrons, and particles (protons). Electrons are rarely used as they have poor penetration through the cranium. Photons and particles are delivered as focused beams aimed at the tumor from varying angles. By far most commonly used are photons, which are usually generated using a linear accelerator to accelerate electrons which strike a target and result in the release of a focused beam of photons. Cobalt-60 is the second most commonly used source of photon radiation in the treatment of intracranial tumors. It is rarely used in the United States and Western Europe because its low beam energy makes it difficult to treat deeply seated tumors. Protons are the most commonly used particles, also generated in accelerators. Because of their high initial cost, there are very few dedicated clinical proton facilities in the world, and the treatment cost compared with photon therapy is currently estimated to be at least double. Protons originally held significant promise in the 1980s because of their (at that time unique) ability to achieve very spatially conformal dose distributions while sparing normal tissues. The advent of photon IMRT (discussed below) in the 1990s effectively eliminated this advantage. There are no prospective randomized studies demonstrating that one modality is inherently superior to the other in the ability to safely deliver a desired dose to a specified target, marketing efforts of various vendors notwithstanding.

Absorbed dose is measured in Gray (1 Gy = 100 cGy; 1 cGy = 1 rad in the old nomenclature). Dose is prescribed at a percent isodose line (IDL), which is the line
encompassing the target on a two-dimensional image along which the delivered dose is the same at every point. (In three dimensions, the term “isodose cloud” is used.) The percent IDL is referenced to the dose at a particular point, often the geometric center of the target.

**Fractionated and Single-Dose Treatments**

Radiation therapy can be delivered in multiple treatments (“fractions”) or in a single treatment. “Radiosurgery” specifically refers to the delivery of a large single dose of radiation given in a highly focused manner to a well-delineated target using a three-dimensional Cartesian coordinate system for targeting. If more than one fraction is delivered in this manner, it is termed “fractionated stereotactic radiation therapy.” This method is expected to produce the same biological effect as a course of several weeks of fractionated radiation therapy (4). Comparisons of outcomes between fractionated and single-dose treatment are described below under Section III for each applicable diagnosis. In general, the risk-benefit ratio drives the choice of therapy. Only when efficacy and safety are similar does convenience become the deciding factor.

**Conformal Treatment**

The basic rationale for using conformal delivery is to spare adjacent normal tissue from receiving unnecessary radiation, the ramifications of which are discussed in Section II below. 3DCRT refers to a specialized situation in which the volumetric distribution of the desired dose (isodose cloud) accurately mimics the shape of the target. Both fractionated radiation therapy and radiosurgery may be delivered in this fashion. IMRT is a subset of 3DCRT delivery; the intensity of the photon flux within the treatment field(s) is modulated during each treatment, resulting in a non-uniform dose distribution. IMRT is frequently “inverse-planned,” that is, dose constraints of target tissues are predefined by the clinician and the treatment planning software optimization algorithm generates a plan to meet those goals. This often results in a more conformal dose distribution to the target and better sparing of select adjacent dose-limiting structures. The trade-off is that a larger volume of normal tissue receives a very low dose of radiation, the late effects of which are not fully understood. A similar effect can be achieved with protons by varying the depth of the Bragg peak, the point in the tissues at which these particles deposit the majority of their therapeutic energy.

**Stereotactic Treatment**

The term “sterotactic” refers to a specialized method of targeting the three-dimensional treatment (whether fractionated or radiosurgery) whereby the target lesion is referenced not to the patient but to a reproducible x,y,z coordinate system. This method of targeting is used when a very high degree of accuracy and precision is required, because the coordinate system is affixed (usually invasively) to the patient. The Leksell neurosurgical headframe is the most common example of such a device. It immobilizes the patient’s head and provides the reference coordinate system required for targeting. In general, any type of treatment can be delivered stereotactically. A number of other stereotactic systems have been derived from this concept, including a system of implanted screws to which a headframe can be reproducibly fixed and removed (5,6), a system that utilizes implanted fiducial markers which are then tracked in real time by a camera (6), a non-invasive system using an infrared-detectable diode array attached to a bite block (7–10), and a relocatable non-invasive stereotactic headframe (11–14). Practically speaking, stereotactic delivery is useful when extremely tight margins of error are required because critical normal structures are extremely close to a well-demarcated target and would otherwise receive an excessive dose of radiation. Stereotactic targeting is considered mandatory for radiosurgery, because there is only one fraction, in other words, only one opportunity to “get it right.”

**Image-Guided Treatment**

IGRT is the newest development in radiation delivery systems. The treatment of intracranial lesions is based on three-dimensional volumetric data sets obtained from CT and MRI to delineate the target for the computer-aided planning and simulation of treatment. True IGRT acquires another three-dimensional volumetric data set at the time of treatment delivery, ideally using the treatment machine itself to confirm that the target is localized correctly with respect to the radiation beams (15). This is useful when dealing with targets that may have shifted during the time between treatment simulation and treatment delivery. Such shifting rarely applies to intracranial lesions. Some devices advertised as “imaged guided” obtain only a set of orthogonal X-ray films for localization of the target center, lacking the true spatial information of a three-dimensional data set. Such films do not permit subtle corrections of position at the time of treatment.

**The Machines**

There are many treatment machines on the market. A brief list of the most common device trade names and their manufacturers follows. It will undoubtedly be partially out of date by the time this article appears. The Leksell Gamma Knife (Elekta, Stockholm, Sweden) in its traditional configuration uses 201 stationary cobalt sources to deliver a single focused ellipsoid sphere of radiation dose with a mechanical reproducibility of ≤0.2 mm, making it the gold standard in terms of accuracy and precision (16)
Fig. 1. The newest configuration of the device (Perfexion) uses fewer sources to achieve a higher degree of conformity than previously possible. The Cyberknife (Accuray, Sunnyvale, CA) is a small linear accelerator mounted on a robotic arm. It can focus a single photon beam of fixed shape at a tumor from a wide variety of angles. This system incorporates orthogonal imaging for two-dimensional IGRT (17). The Synergy and Axesse (Elekta) represent standard-size medical linear accelerators mounted on rotating gantries that, in combination with a moving table, can deliver a photon beam that can be shaped and have its flux modulated (Fig. 2). This system incorporates CT for three-dimensional IGRT (15). The Trilogy (Varian, Palo Alto, CA) is a standard-size medical linear accelerator rotating on a fixed axis that, in combination with a moving table, can deliver a photon beam that can be shaped and have its flux modulated. This system incorporates orthogonal imaging for two-dimensional IGRT. The Novalis (BrainLAB, Feldkirchen, Germany) is a dedicated stereotactic linear accelerator. Proton beam facilities (Optivus Technology, Inc., San Bernardino, CA; Ion Beam Applications, Louvain-la-Neuve, Belgium) consist of very large gantry-mounted single-beam delivery systems and mobile patient tables to deliver a focused particle beam from a wide variety of angles.

With these tools, a wide variety of treatment options can be tailored to patients’ particular diagnoses, such as fractionated stereotactic IMRT or IGRT. Each device vendor claims to have the superior technology. The effect is that patients shop around for technology they have seen advertised regardless of its appropriateness to their condition. The concern is that “hype” about devices may result in the inappropriate use of a particular device for a specific indication when another device may have been better suited.

COMPLICATIONS

The risk of complications typically depends on three parameters: the organ at risk (OAR) receiving the dose, the total dose received, and the dose delivered per fraction. The decision to select a particular treatment from several of similar efficacy will be heavily based on the risk profile.

Fractionated Treatment

With fractionated radiation therapy, the absolute incidence of damage to the optic chiasm and nerves is 0.3% at doses \( \leq 60 \) Gy, as long as the daily fraction size is kept below 2 Gy. At 10 years, patients treated with daily doses of 180 cGy to a total dose of 45 Gy can expect no risk of visual impairment from therapy, and most recent series report no symptomatic visual injury below 55 Gy (18).

Single-Dose Treatment

With single-dose radiosurgery, injury to the optic apparatus is highly dose-dependent, with 0–2% incidence of optic neuropathy at doses below 10 Gy, a 27% incidence at doses between 10 and 15 Gy, and a 78% incidence at doses above 14 Gy (19). Thus, tumors in very close proximity (<2–3 mm) to the optic chiasm and optic nerves may not be suitable targets for single-fraction radiosurgery. Depending on diagnosis, typical doses delivered will range from 10 to 25 Gy.

THE TUMORS

Optic Glioma

In general, patients with visual pathway gliomas (VPGs) do not die from the local effects of their tumors and cause-specific survival rates approach 100%. Therefore, the
multidisciplinary management of VPGs emphasizes minimizing the sequelae of treatment. Radiation therapy results in 10-year survival rates ranging from 40% to 93% but at significant potential cost to young children (20–25). Risks may include endocrine disorders, neurodevelopmental disorders, moyamoya syndrome, and second malignancy. These risks are significant enough that children of any age should be treated with chemotherapy alone, delaying the use of radiation therapy until progression is documented (26). Typically a median delay of 2.5–3 years can be achieved using this approach, with 5-year progression-free and overall survival rates of 56% and 90%, respectively (27–29). When radiation therapy is required, typical doses range from 45 to 60 Gy in 1.8- to 2.0-Gy fractions (30,31). Prospective randomized phase III trials have shown that non-VPG low-grade gliomas do not exhibit a radiation dose response; that is, higher doses do not result in improved outcomes (32,33). Thus, most clinicians extrapolate from these data when treating VPGs, preferring to use doses in the lower end of this range.

Three-dimensional treatment planning is mandatory to minimize dose to uninvolved structures. However, stereotactic positioning is not required even if the tumor is close to an uninvolved contralateral optic nerve, because at 45 Gy in 1.8-Gy fractions, the (admittedly statistical) risk of treatment-induced optic neuropathy is zero (34,35). Moyamoya syndrome develops in 3.5% of children after cranial irradiation, with patients with neurofibromatosis type 1 (NF-1) having a 3-fold higher risk than patients without this diagnosis (36,37). Increasing radiation dose is associated with a higher risk of moyamoya syndrome; 50% of patients experience its onset more than 4 years after treatment. The use of IMRT in children is controversial, because it potentially delivers a low dose of radiation to a large intracranial volume, which hypothetically could increase the risk of late malignancy. Radiosurgery has no defined role in the management of this disease.

Meningioma

The diagnosis of meningioma can be reliably made in most cases by a classic MRI appearance. The classic findings include a dural-based extra-axial lesion often manifesting a dural tail. The lesions usually enhance brightly and homogeneously. Benign tumors rarely have necrosis associated with them because they are slowly growing. Patients with multiple meningiomas or (or schwannomas) should undergo a workup for neurofibromatosis type 2; multiple dural-based lesions could also be metastatic (38,39). The factors that predict meningioma recurrence include subtotal resection, optic nerve sheath location, ≥4 mitoses per high-power field, male gender, age <40 years, and microscopic brain invasion (40,41). Respectively, average 5-year and 10-year progression-free survival rates are 88% and 75% for patients with a gross-total removal (GTR) and 61% and 39% for patients who have less than a GTR (41–43). The five-year recurrence rate after resection for benign meningioma is 12%, for atypical meningioma is 41%, and for brain-invasive meningioma is 56% (44).

Most authors now recommend fractionated radiation therapy for definitive management of optic nerve sheath meningiomas (45,46). For all intracranial benign (World Health Organization [WHO] grade I) meningiomas, doses at or above 50–53 Gy in conventional fractionation are required for durable control (47–49). There are no useful data to suggest that encasement of the optic nerve by a nerve sheath meningioma is a contraindication to radiation therapy. Stable or improved visual fields and visual acuity can be expected in 95%–100% of patients treated with definitive radiation therapy, from which this author infers that tumor control is the primary factor in maintaining functional vision (46,50–52). Atypical features are found in approximately 5%–20% of intracranial meningiomas and are indicative of a more aggressive biologic potential (44,53). Local recurrence rates for patients with atypical meningiomas are higher than the rates for those with benign tumors, (40% at 5 years (44,54)), and it is common practice to offer patients with atypical meningiomas adjuvant irradiation. Most authors recommend 54–60 Gy for WHO grades II–III (49,55,56).

Radiosurgery is one of the standards of care for well-circumscribed WHO grade I intracranial meningiomas (57). It is not considered definitive therapy for WHO grade II or higher grade lesions because of the high risk of failure outside the treated volume (58). Thus, for higher-grade lesions, radiosurgery should be considered only
a temporizing measure or as palliation after failure of conventional fractionated radiation therapy. Local control rates are similar to those seen with GTR, subtotal resection followed by radiation therapy, or definitive radiation therapy (58,59). Most authors advocate doses of 11–18 Gy at the isodose prescription line encompassing the tumor volume (marginal dose) (57,59–63). It is recommended that the optic chiasm and nerves receive no more than 10 Gy to any segment (19,64). This practice keeps the risk of symptomatic optic neuropathy to 2% or less. At the doses required to treat meningiomas, the incidence of optic neuropathy rises to 27% (see Section II) and radiosurgery is thus not typically considered standard therapy for optic nerve sheath meningiomas.

Particularly challenging is the management of the subtotally resected meningioma. Overall, one third of intracranial meningiomas are not fully resectable (43). The extent of surgical resection as defined by Simpson (64) is related to the local recurrence risk, with 5-year, 10-year and 15-year recurrence rates of 7%–12%, 20%–25%, and 24%–32%, and second operation rates of 6%, 15%, and 20%, respectively, among patients with GTR (41–43). Recurrence rates after subtotal resection (STR) are substantially higher (65). Overall, approximately 40%–50% of patients with STR who do not receive adjuvant therapy develop local progression within 5 years, 60%–83% within 10 years, and at least 70% within 15 years (42,66,67). Patients with subtotally resected atypical tumors achieve 5-year relapse-free survival rates of 48% with fractionated radiation therapy and 83% with radiosurgery, respectively (58,68). Although not randomized, these comparisons suggest that patients with subtotally resected meningiomas should be offered the option of additional treatment.

**Pituitary Adenoma**

The multidisciplinary management of pituitary adenoma is complex and controversial, without prospective trials to provide guidance. A conservative single-institution treatment algorithm is shown in Figure 3. In general, the treatment of choice for large tumors presenting with mass effect is surgical resection, potentially followed by fractionated radiation therapy or single-dose radiosurgery. [Some institutions prefer to withhold radiation therapy until progression after initial resection (69)]. The intent of radiation therapy/radiosurgery is control of tumor growth and hormone hypersecretion, not eradication of tumor mass. Although radiation therapy alone is effective in selected patients, surgical decompression plus postoperative irradiation provides better results in patients with moderately advanced visual field deficits. With very large invasive tumors for which radical removal would be associated with a high mortality and morbidity, reliance should be primarily on radiation therapy, although subtotal resection may be required as an urgent debulking measure if vision is severely compromised.

Pituitary adenomas show dose-response rates that are dependent on tumor type. Nonfunctioning tumors are usually controlled with 45–50.4 Gy of conventionally fractionated external beam radiation therapy or stereotactic radiosurgery delivering 20–25 Gy to the tumor margin, with control rates in the 95% range. Functioning tumors require slightly higher doses, typically 50–54 Gy of conventionally fractionated external beam radiation therapy or stereotactic radiosurgery delivering 25–30 Gy to the tumor margin. Control rates are slightly lower than for nonfunctioning tumors (70–89). A summary of dosing guidelines is shown in Table 1. Uncommonly used forms of radiation therapy include proton and α-particle radiation therapy and implantation of radioactive sources (90Y or 198Au). Like stereotactic radiosurgery, these methods also attempt to deliver very large doses to highly restricted volumes within the pituitary gland. Their application is thus limited to small, essentially intrasellar tumors.

**Craniopharyngioma**

Because radical surgical resection of craniopharyngioma is associated with a high rate of visual loss and impaired hormone function requiring replacement therapy,
Orbital Pseudolymphoma (Lymphoid Hyperplasia) and Lymphoma

Orbital pseudolymphomas are benign masses of lymphoid hyperplasia localized to the orbit. True orbital lymphomas present as painless, slowly enlarging lesions arising from the eyelid, orbit, lacrimal gland, or conjunctiva; 75% are unilateral. Orbital lymphoma is the most common primary orbital malignancy (55%) It may represent the only manifestation of the disease (96,97) or be part of multicentric systemic lymphoma, with 31% of lymphoid tumors of the conjunctiva associated with systemic lymphoma (98). Hence, the diagnosis requires a biopsy and systemic staging workup. Fifteen percent of patients with localized orbital disease subsequently develop systemic lymphoma (97). The risk of disseminated disease is related to histology and location. Thus, lymphomas of the conjunctiva or deep orbit have the lowest risk of dissemination (21%–24%) compared with 38% for the lacrimal gland and 50% for the eyelid (99). Good prognostic features are complete remission in response to initial treatment, primary radiotherapy, and older age (100).

Orbital radiation therapy is highly effective in eradication of orbital lymphoma. A dose of 20–40 Gy is used for pseudolymphoma and low-grade lymphoma; 30–50 Gy is used for high-grade lymphoma (100–104). Five-year survival rates range from 70% to 89% for patients with pseudolymphoma and low-grade lymphoma (105). The five-year survival rate is only 33% for those patients with high-grade lymphoma (103). Recurrence after radiation therapy is 25% for low-grade and 75% for intermediate- and high-grade lymphomas. The addition of chemotherapy (usually R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone]) to radiation therapy reduces the risk of recurrence to 33% for intermediate-grade and 50% for high-grade lymphomas (106). Thus, radiation therapy as single-modality treatment should be reserved for low-grade localized tumors. Disseminated and secondary orbital lymphomas are often treated with chemotherapy alone.

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The Human Resource Crisis in Neuro-Ophthalmology

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**Abstract:** Neuro-ophthalmology is facing a serious human resource issue. Few are entering the subspecialty, which is perceived as being poorly compensated compared with other subspecialties of ophthalmology. The low compensation comes from the fact that 1) non-procedural encounters remain undervalued, 2) efforts that benefit other medical specialists are not counted, and 3) the relatively low expenses of neuro-ophthalmologists are not factored into compensation formulas. Mission-based budgeting, which forces academic departments to be financially accountable without the expectation of fiscal relief from medical schools or practice plans, has exacerbated the compensation issue. Solutions must come from within neuro-ophthalmology, academic departments, medical schools, and medical practice plans. They include 1) providing educational resources so that neuro-ophthalmologists need not spend so much time teaching the basics, 2) factoring into compensation the impact of neuro-ophthalmologists in teaching and on revenue generation by procedure-based specialists, 3) improving the efficiency of neuro-ophthalmologists in their consultative practices by providing ample clerical support and other measures, 4) providing contractual salary compensation by departments such as neurosurgery to recognize the contributions made by neuro-ophthalmologists, and 5) reorganizing the academic clinical effort as multidisciplinary rather than departmental.


In 2004, Peter McDonnell, MD wrote an article in *Ophthalmology Times* regarding how training and patient care might suffer if the human resource issues in neuro-ophthalmology were not addressed (1). The article was an alert to the looming crisis of retention and recruitment of neuro-ophthalmologists for academic departments of ophthalmology. His article prompted me to write an editorial in *Ophthalmology* (2) that proposed remedies. My view is that human resource issues can be solved by allowing the discipline to remain respected and by making it financially viable.

**HUMAN RESOURCE ISSUES**

The North American Neuro-Ophthalmology Society (NANOS) and the American Academy of Ophthalmology (AAO) have developed unpublished data suggesting that, based on past usage patterns, the United States needs approximately one full-time equivalent (FTE) clinical neuro-ophthalmologist per 1.2 million people or 250 FTE neuro-ophthalmologists. We estimate that there are now 200 FTE neuro-ophthalmologists, which explains why most of us are so busy. Assuming that the average person practices 35–40 years after completing training, we will lose 5–7 FTE neuro-ophthalmologists each year.

An unpublished NANOS survey has suggested that neuro-ophthalmologists spend about 50% of their time in clinical neuro-ophthalmology. So if we lose 5–7 FTE per year, we will need to train 10–14 replacement neuro-ophthalmologists per year (assuming that they remain in the United States and devote 50% of their professional time to the practice of neuro-ophthalmology). Over the past several years, we have been well below this replacement level, training approximately 5 neuro-ophthalmologists per year. Not only must these trainees examine patients, but they must also train the next generation of neuro-ophthalmologists.

**SHORTAGE OF NEURO-OPHTHALMOLOGIST TRAINEES**

Why are fewer people training in neuro-ophthalmology? There is no apparent lessening in passion for the discipline. Most trainees interviewed consider it as fascinating and professionally rewarding as ever. The problem is rather that the role a neuro-ophthalmologist is typically asked to play...
in an ophthalmology department is not in concert with the financial reality of academic neuro-ophthalmic practice, which in turn is based upon the undervaluation of “cognitively based” (non-procedural) encounters. There is also a perception that neuro-ophthalmologists must give up surgery to avoid competing with other ophthalmology department members and referring doctors and to build a consultative practice. The mismatch between the expectations in terms of job description and financial performance often leads to neuro-ophthalmologists doing everything demanded of them yet judged as underperforming financially.

Most ophthalmologists who elected a career in academic neuro-ophthalmology did so knowing that they would be receiving less income than their colleagues. But the reimbursement gap has been growing. The application of more quantitative measurements of financial performance within ophthalmology departments increasingly leads to a false perception that neuro-ophthalmologists are not providing enough value. Some report that they have to beg to receive reasonable compensation even if they are working very hard.

This development is partly the result of a payment method biased toward procedures. In a medicine department made up almost entirely of non-surgeons and in which most of the medical practice is consultative, this devaluation of non-procedural effort is not a problem. But in procedure-based departments such as ophthalmology, the lower accrual of relative value units (RVUs) by neuro-ophthalmologists may be misconstrued as producing less relative value.

Some years ago, there seemed to be a trend toward developing a higher proportion of neuro-ophthalmologists trained in neurology rather than ophthalmology and that this development might solve the human resource problem. But as neurologists have developed procedures (sleep studies and video electroencephalograms), the same financial factors have cropped up in those departments, and they are keeping people from choosing a career in neuro-ophthalmology. For whatever reason, the percentage of NANOS members who are neurology-trained has not significantly risen in the past several years, so there is not much evidence that neurology-trained neuro-ophthalmologists will be a viable option for academic departments of ophthalmology.

**MISSION-BASED BUDGETING**

The financial issue became intensified as mission-based budgeting (MBB) came to be adopted in U.S. medical schools in the past 10 years. MBB organizes revenue and expense accountability by the department rather than by the medical school or by overall clinical effort. There is a discrepancy here. The delivery of health care in the academic health care center, or elsewhere, is often not organized by department. The amount of interdisciplinary effort has been increasing markedly, particularly as concerns neuro-ophthalmologists. Their maximal financial impact is often in departments other than their “home” department, where their financial accountability is measured. So even when the clinical enterprise as a whole perceives a financial benefit from neuro-ophthalmologists, their home departments may not see this benefit.

MBB is often blind to downstream revenue. Academic medical centers do not do a good job of tracking admissions or procedures that one faculty member generates for another service. For example, when neuro-ophthalmologists send third cranial nerve palsy patients for aneurysm treatment, which generates a large revenue for another department, they receive no credit.

**BILLING CODES**

Another issue is the undervaluation of neuro-ophthalmologists’ work in the RVU system, which has become a standard in computing reimbursement. Years ago there was a move to create level 6 and 7 consultation codes to reward the intensive work performed by specialties such as neuro-ophthalmology. That move has stalled. As a result, neither the work done during the patient visit nor the follow-up and coordination of care with other specialists is compensated. For example, the time spent by neuro-ophthalmologists in reviewing brain images, for which the radiologist is amply compensated, does not typically enter into the neuro-ophthalmologists’ reimbursement.

**EXPENSE ACCOUNTING**

Another financial issue is that ophthalmology departments often base salary compensation on a fixed percentage of collections from patient consultations. The expenses incurred by the individual physician are often not factored in. The typical neuro-ophthalmic practice requires relatively low examination room usage and technician and receptionist support and less capital equipment. Other department members who have shorter encounter times often require much greater equipment and personnel resources to run several examination rooms, as well as more capital equipment for their practices. Furthermore, the surgical members of an ophthalmology department generate much of their revenue in the operating room, the expenses for which they are never charged!

In the past, when reimbursements were relatively high for all medical practices, department chairs had ample funds to compensate the non-procedural members of the department. But as reimbursements have dropped across all ophthalmic service lines, this traditional solution is no longer viable.
MEASURING VALUE

Ophthalmology departments need neuro-ophthalmologists for reasons that go far beyond the requirements of the accrediting bodies. Not having a neuro-ophthalmologist would have a ripple effect upon the ability of others in the department to generate revenue. Here is how.

As MBB has made clinical time expended equate with money lost, patient throughput has become paramount, and the theme is often to shunt the patients with complex problems to the neuro-ophthalmologists. As neuro-ophthalmologists do not have other activities that yield higher revenue per unit time, they are viewed as the least expensive method of handling these patients to increase the throughput of the rest of the department members. So here is a hidden value of neuro-ophthalmologists. In accepting time-consuming cases from other members of the department, they free up their colleagues’ time for revenue-generating activities. How many fewer retinal procedures would be performed if retinal surgeons had to be out evaluating the patients with cone and rod dystrophy and those with unexplained visual loss who are initially sent to them for consultation?

According to a colleague of mine, one ophthalmology department has apparently calculated, in an unpublished study, that its intradepartmental referrals to neuro-ophthalmology freed up the other members of the department for 1,200 more visits per year in their own specialties, yielding significantly greater revenues for all other department members.

Finally, in many departments of ophthalmology, neuro-ophthalmologists have a heavy teaching role. The first four winners of the AAO’s prestigious Straatsma award were neuro-ophthalmologists. This non–revenue-generating role is not acknowledged when RVUs are totaled.

SOLUTIONS

To ensure the viability of neuro-ophthalmology and other non-procedural specialties, some reform of revenue or expense valuation must occur. Solutions must come from three sources: NANOS, departments of ophthalmology, and the medical schools or clinical practice plans.

Attracting neuro-ophthalmologists. NANOS can help by showing residents who have not committed to a specialty what neuro-ophthalmology is. The society is sponsoring travel grants to five residents per year so that they may attend the annual NANOS meeting. NANOS has also initiated young member programs, and last year started a young investigator grant program that will provide one to two members a year with seed funding for research.

Decreasing the time required of neuro-ophthalmologists to discharge teaching duties. NANOS is doing this by expanding educational resources and by developing and publishing a curriculum for neuro-ophthalmology. With funds from the National Library of Medicine, Pfizer Pharmaceuticals, and the NANOS membership itself, NANOS has built a hefty online resource library entitled the Neuro-ophthalmology Virtual Education Library (NOVEL). (See NANOS News feature in this issue of the Journal.) NANOS is also joining educational forces with the American Academy of Ophthalmology (see NANOS News feature in the June 2008 issue of the Journal).

Practicing something in addition to neuro-ophthalmology. NANOS is encouraging those interested in a career in neuro-ophthalmology to consider blending it with orbital work, pediatric ophthalmology, glaucoma, or a residency training program directorship. This tactic has been part of the discussions by the Neuro-ophthalmology Fellowship Certification Committee. A consequence of this strategy will probably be that we will need more neuro-ophthalmologists in absolute numbers to achieve the same number of FTEs, as each individual devotes less time to neuro-ophthalmology. An unintended consequence could be that neuro-ophthalmic knowledge and skills would fall below a critical level.

Educate neuro-ophthalmologists in appropriate visit coding. This is an area in which neuro-ophthalmologists have been traditionally ignorant. Consider Code 99358, used for reviewing records, telephone consultations, and coordination of care with other specialists. This activity usually takes place when the patient is not present but could be compensated.

Reduce neuro-ophthalmic examination time. The traditionally low throughput of neuro-ophthalmologists can be remedied somewhat. For example, lengthy history-taking can be reduced by having the patient complete a mailed or online history form before the visit. The labor of gathering laboratory tests and imaging results can be delegated to a clerk or technician.

Redistributing patient revenues. Compensation models could include redistributing pools of funds to lower earners. Recognizing that spine surgery generates much more revenue than cranial surgery, some neurosurgery departments have spine surgeons contribute a relatively large percentage of their earnings to a common pool.

Fairer computation of practice expenses. This may be achieved by charging neuro-ophthalmologists a reduced percentage for overhead, reflecting the lesser personnel and equipment use by a neuro-ophthalmic practice, a method already used by some ophthalmology departments.

Bonus for teaching and other service. If departmental revenue is allocated based upon RVU generation, RVU credits can be granted to neuro-ophthalmologists for disproportionate teaching or committee service.

Compensation based on “downstream revenue generation.” The medical school or practice plan must try to track downstream revenue. In doing so, attention must be paid to Stark and anti-self referral laws. Departments that
benefit from neuro-ophthalmologists’ efforts could financially underwrite those efforts. One example would be to shift the time costs of obtaining pre-authorizations for neuro-imaging to radiology departments, pursuant to local legal review.

Neurosurgery departments could agree to reimburse neuro-ophthalmologists’ home departments for providing services. Neurosurgeons understand well the benefit that neuro-ophthalmologists bring to their practices in terms of quality and time freed up to spend in the operating room.

Medical schools should consider recognizing and compensating cross-departmental education. Neuro-ophthalmologists may be asked to lecture in several departments, but may only get credit for their activities in their home department.

Moving neuro-ophthalmologists to another “home department.” Departments of neurosurgery could become the home departments for neuro-ophthalmologists.

Reorganizing revenue and expense generation by non-departmental entities. Medical practice plans could be organized as multidisciplinary rather than traditional departmental entities. In that way, neuro-ophthalmologists, as all “orphan specialties,” would become the expense of the whole group, thereby better aligning incentives, expenses, and revenue.

CONSEQUENCES OF IGNORING REFORM

There is some urgency in addressing the financial barriers to retaining and recruiting neuro-ophthalmologists. There are now fewer than 2 FTE neuro-ophthalmologists per medical school or ophthalmology department. (unpublished NANOS survey data). If 6 FTE neuro-ophthalmologists are lost each year to retirement in the United States, and only about 2 FTEs replace them, there will be 4 fewer FT academic neuro-ophthalmologists each year. This dearth will make it difficult for departments to meet their training and service needs.

This analysis actually underestimates the human resource crisis in neuro-ophthalmology, as there is now an exodus of established neuro-ophthalmologists from academic departments. An unpublished 2008 survey of neuro-ophthalmic practice economics by NANOS disclosed a large disparity between the relatively higher earnings of neuro-ophthalmologists in community practice and those of their colleagues in academic practice. Community practitioners reported 80% greater mean income. This discrepancy is present despite the fact that neuro-ophthalmologists in academic practice are working more hours than those in community practice. This reality, coupled with the deteriorating financial environment for academic neuro-ophthalmologists in ophthalmology departments, is likely to hasten the day when we do not have an adequate number of neuro-ophthalmologists to train the next generation. I hope that creative solutions, such as those described herein, will be applied before that day comes.

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Positive Apraclonidine Test Within Two Weeks of Onset of Horner Syndrome Caused by Carotid Artery Dissection

Horner syndrome, manifested by ipsilateral miosis, upper lid ptosis, and sometimes facial anhidrosis, is caused by disruption of sympathetic innervation to the eye and face (1). Lack of pupil dilation after instillation of cocaine, an indirect sympathomimetic (2), has been traditionally used to support a clinical diagnosis of Horner syndrome (1). However, cocaine has the disadvantages of high cost, poor dilating capability, and lack of ready availability (3).

Topical 0.5% or 1% apraclonidine (Iopidine; Alcon, Fort Worth, TX) has recently been proposed as a substitute for cocaine in testing for Horner syndrome (4–12). Although apraclonidine is primarily an $\alpha_2$ agonist, it also has weak affinity for $\alpha_1$, the predominant receptor in the iris dilator muscle (13). Sympathetic denervation in Horner syndrome results in upregulation or increased sensitivity of $\alpha_1$ receptors (14). Topical apraclonidine dilates a sympathetically denervated iris but not a normally innervated iris.

However, the latency between sympathetic damage and development of upregulated adrenergic iris receptors is uncertain. In previous reports, patients had long-standing Horner syndrome before the application of the apraclonidine test (4–12). The shortest documented latency from occurrence of the lesion to a positive apraclonidine test is 1 month in a patient with “carotid stenosis” (5). We report a patient who developed a Horner syndrome acutely from carotid artery dissection who had a positive apraclonidine test within 2 weeks of symptom onset.

A 36-year-old man was “cracking his neck” as a customary practice when he heard a loud popping sound in his neck. He immediately developed right-sided headache and right posterior neck pain. A coworker noted that the patient’s right upper eyelid was droopy and that the right pupil was relatively small. Ten days after onset, he presented to a hospital emergency room and was transferred to our care with a clinical presumption of right Horner syndrome. Head and neck computed tomographic angiography (CTA) and catheter-based carotid angiography (Fig. 1) showed tapered narrowing of the right internal carotid artery of 2.5 cm extending from the carotid artery bifurcation to the skull base in a configuration typical of dissection.

We examined the patient 14 days after symptom onset. Visual acuity was 20/20 in both eyes. There was 1 mm of right upper lid ptosis with good levator function. In dim illumination, the pupils measured 2 mm on the right and 3 mm on the left with both pupils constricting adequately to direct light (Fig. 2). The anisocoria was more apparent in dim illumination. There was no relative afferent pupillary defect. Results for the remainder of the ophthalmic and neurologic examinations were normal.

Thirty minutes after instillation of one drop of apraclonidine 0.5% in both eyes, the right pupil measured 5 mm and the left pupil measured 3 mm in dim illumination (Fig. 2). The right upper lid ptosis disappeared.

Because our patient’s manifestations of carotid artery dissection had such abrupt onset, we can accurately date the latency from the time of sympathetic damage to the performance of the apraclonidine test as being no more than 14 days. Apraclonidine testing in Horner syndrome has been reported to have been administered in 65 patients. The documented latency of a positive test after sympathetic damage ranges between 1 month and 10 years (4–12). The sensitivity of the apraclonidine test for Horner syndrome is still unknown. Among the patients tested with apraclonidine (using cocaine as the pharmacologic gold standard), two false-negative results have been reported.

FIG. 1. Right carotid catheter angiography shows tapered narrowing (arrow) of the right internal carotid artery consistent with dissection.
and an additional three patients have shown reversal of the anisocoria only in bright illumination (6). One explanation for false-negative test results has been the unknown latency required for up-regulation of $\alpha_1$ receptors. The false-negative results occurred, however, in patients who had had clinical evidence of Horner syndrome for a minimum of 6 months. Wider studies will need to be performed to determine the shortest latency and the reliability of the apraclonidine test in the diagnosis of Horner syndrome.

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**Transient Anisocoria Caused by Aerosolized Ipratropium Bromide Exposure From an Ill-Fitting Face Mask**

Transient anisocoria caused by aerosolized ipratropium bromide from an ill-fitting face mask is apparently a well-described entity (1-7), but is still not immediately recognized. We report such an occurrence.

A 52-year-old man with chronic obstructive pulmonary disease and depression was transferred to our institution for further management of a biliary leak due to laparoscopic cholecystectomy. Physical examination on admission showed a distended abdomen with absent bowel sounds. Twenty-four hours later, he developed acute hypercapnic respiratory failure that required noninvasive ventilation with bilevel positive airway pressure (BiPAP). During morning rounds, his right pupil was found to be fixed and dilated. No other abnormalities were noted on neurologic examination.

Results of emergency brain CT were normal. Further review disclosed that he had received nebulized albuterol and ipratropium bromide via a face mask that was attached...
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Optic Neuritis as the First Manifestation of Rheumatoid Arthritis

Optic neuritis has been rarely reported in patients with rheumatoid arthritis (RA) and never as the initial manifestation in a patient who lacked any clinical evidence of RA until years later. We report a patient with optic neuritis as the initial presentation of RA.

A 52-year-old woman without medical problems presented in 1988 to our hospital with sudden left eye visual loss for 3 weeks. Best-corrected visual acuity was 20/25 in the right eye and no light perception in the left eye. Optic disc swelling was present in the left eye. The right eye visual field was normal.

Laboratory studies showed a normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Normal results included tests for antinuclear antibodies (ANAs), rheumatoid factor (RF), C3, and C4. Orbit CT
revealed no abnormalities. Despite oral corticosteroid treatment for presumed optic neuritis, visual acuity of the left eye did not recover.

In 1995 she complained of poor vision of the right eye for 3 days. Best-corrected visual acuity was 20/200 in the right eye and no light perception in the left eye. The right optic disc was normal, and the left optic disc was pale. She read none of the Ishihara color plate. Automated perimetric examination revealed a nasal upper quadrant defect. Brain CT was normal (MRI was contraindicated because of residual bomb chips in her abdomen and mediastinum). ESR and CRP level were normal, the RF level was elevated and results for ANA were positive, with normal levels of C3 and C4. Pulse therapy with methylprednisolone produced recovery to 20/20 and a normal visual field in the right eye.

In 1999, she developed arthralgia and symmetrical swelling with morning stiffness over the proximal interphalangeal joints and carpal bones of both hands. Plain x-rays of the both hands showed periarticular swelling in the proximal interphalangeal joints and relatively osteoporotic changes of carpal bones. She had an elevated RF level and a positive results for ANAs. RA was diagnosed according to the clinical classification criteria for RA (1). She began treatment for this condition.

In 2006 she reported acute blurred vision of the right eye again for 3 days but no exacerbation of rheumatologic symptoms. Best-corrected visual acuity of the right eye was finger counting. No optic swelling of the right eye was found. Perimetry of the right eye revealed nerve fiber bundle defects. RF level and test results for ANAs were normal, but her test results were positive for anti-Ro and anti-La antibodies. Pulse therapy with methylprednisolone produced recovery of visual acuity in the right eye to 20/20 but both optic discs were now pale (Fig. 1) and visual field loss persisted.

Optic neuropathy was first reported in RA in 1980 (2). Autopsy showed necrotizing vasculitis of the right posterior ciliary artery and lymphocytic vasculitis and perivasculitis of the left posterior ciliary artery (2). Approximately 25% of patients with RA have vasculitis with involvement in all sizes of veins and arteries on post-mortem examination (2). Occlusion of one of the posterior ciliary arteries or its branches produces ischemic optic neuropathy with a spectrum of changes that results in complete blindness or variable visual field defects (2). Milder optic nerve damage due to a vasculitic mechanism, characterized by demyelination, had a good response to pulse corticosteroid therapy (3). More severe and irreversible cases of optic neuropathy have caused axonal necrosis (3).

In our patient, the first attack of optic neuropathy of the left eye resulted in blindness. Its features are atypical for optic neuritis and more typical of a severe ischemic process. In subsequent attacks affecting the right eye, however, vision did recover and corticosteroid treatment might have made a difference, perhaps by attenuating vasculitis.

Particularly unusual in our patient is the fact that the manifestations of RA appeared 11 years after the first attack of optic neuropathy. We highlight this patient to emphasize that an underlying rheumatologic condition may be occult and that early treatment with corticosteroids of a presumed vasculitis may be vision-saving.

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Transient Third Cranial Nerve Palsy Caused by Sphenoid Sinus Aspergillosis

We recently examined a patient who developed a nearly complete unilateral third cranial nerve palsy attributed to sphenoid sinus aspergillosis. The unusual feature is that the palsy resolved spontaneously within 2 days.

A 78-year-old retired teacher presented with the sudden onset of a ptotic right upper lid and diplopia for 1 day. There was no headache. He had hypertension and chronic renal impairment but no diabetes or head trauma.

Vital signs were normal. Visual acuity was 20/40 in both eyes attributed to cataract. Intraocular pressures were 12 mm Hg in both eyes. In dim light, pupils measured 4.5 mm in the right eye and 3 mm in the left eye. The right pupil was not reactive to light; the left pupil was normally reactive. There was no afferent pupil defect. There was complete right upper lid ptosis and a complete deficit of adduction, supraduction, and infraduction of the right eye with normal incyclotorsion and abduction. Ductions of the left eye were normal. Findings from ophthalmoscopy and the rest of the neurological examination were normal.

Although we recommended emergency neuroimaging, the patient insisted on later admission for personal reasons. Two days later, our examination showed complete resolution of all eye findings, but he reported brief episodes of syncope, mental confusion, and headache.

Complete blood count showed a mild leukocytosis (10.6 × 10^3 cells/μL), and C-reactive protein was 1.37 mg/dL. Erythrocyte sedimentation rate was 35 mm/hr. Brain MRI showed a heterogeneous space-occupying lesion in the right sphenoid sinus and a soft tissue lesion in the basal cisterns and sylvian fissure with low signal intensity on precontrast T1 and enhancement on postcontrast T1. There were also a subdural effusion (Fig. 1). MRA demonstrated no aneurysm.

Transsphenoidal endoscopic biopsy disclosed necrotic tissue with a pathologic diagnosis of aspergillosis (Fig. 2). The patient was given intravenous voriconazole for 3 weeks followed by oral fluconazole. Neurologic symptoms and the original MRI lesions eventually resolved (Fig. 1C).

Transient third cranial nerve palsy occurs in ophthalmoplegic migraine (1,2), pseudotumor cerebri (3,4), arteriovenous malformation (5), cryptococcal meningitis (6,7), basilar or posterior communicating artery aneurysm (8,9), and thiazide-induced glucose intolerance (10). It has not been reported in sphenoid sinus aspergillosis.

The transient nature of our patient's third cranial nerve palsy is curious. A possible explanation is that the nerve was initially compressed by localized sphenoid inflammation; perhaps as the pathogen broke through the sphenoid bone and invaded the contiguous basal cistern, the tension of compression was released, allowing spontaneous resolution of the palsy but development of other neurologic deficits.

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FIG. 1. Pretreatment postcontrast T1 axial (A) and coronal (B) MRI shows enhancing soft tissue lesions with low central signal intensity in both sylvian fissures, the prepontine cistern, and the right sphenoid sinus (A, arrow). One month after systemic antifungal treatment, postcontrast T1 MRI (C) demonstrates mucosal thickening with enhancement of the sphenoid sinus mucosa (arrow) and dural enhancement with nodularity (arrowhead).
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Lateral Rectus Muscle Metastasis
As the Initial Manifestation of Gastric Cancer

Four weeks after developing diplopia and right lateral gaze palsy, a 49-year-old man was hospitalized for deep venous thrombosis with pulmonary embolism. Neurologic examination demonstrated orbital swelling, diplopia, and reduced abduction of the right eye. On forced duction testing, there was resistance to passive movement of the right globe. Neck examination was significant for left subclavicular and submandibular adenopathies.

MRI of the brain and orbit revealed diffuse enlargement of the right lateral rectus muscle (Fig. 1A) and the muscle tendon with homogenous enhancement on postcontrast images (Fig. 1B). Upper gastrointestinal tract endoscopy demonstrated moderately to poorly differentiated adenocarcinoma at the gastric body. Right orbital biopsy revealed poorly differentiated carcinoma consistent with a metastasis from the gastric tumor. Despite radiotherapy, the patient died of massive gastrointestinal bleeding approximately 10 weeks after onset of symptom.

Orbital metastasis is uncommon, accounting for 0.07%–4.7% among patients with malignancy (1). Discrete extraocular muscle metastases constitute only 9% of orbital metastases (2). In adults, extraocular metastases originate mostly from cutaneous melanomas and breast and lung carcinomas (2,3). Only rarely do they originate from a carcinoma of the gastrointestinal tract (4).

The majority of patients with metastases to extraocular muscle not only already have a diagnosis of primary malignancy at presentation (2), but also the metastasis occurs late in the course of the systemic malignancy (2). The most frequently affected extraocular muscle is the medial rectus, followed by the lateral rectus, the superior rectus, and the inferior rectus. Bilateral extraocular muscle involvement has
been reported in 17% of patients (2). In our patient, unilateral lateral rectus metastasis was the initial presentation of adenocarcinoma at the gastric body, extending the spectrum of metastatic diseases with a gastric source.

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**REFERENCES**


**Pupillary Autonomic Neuropathy Simulating Partial Horner Syndrome in Diabetes Mellitus and Its Reversal With Control of Blood Glucose**

Horner syndrome, an oculosympathetic dysfunction, which is characterized by a triad of ptosis, miosis, and anhidrosis (1–3), is a rarely reported complication of diabetes (1). We describe a patient who had anisocoria with features of a Horner syndrome as an initial manifestation of diabetes. The anisocoria and supersensitivity to topical apraclonidine resolved with the treatment of hyperglycemia.

A 45-year-old woman was referred to our clinic for a weight gain of 11 kg over the previous 6 months. She had no other symptoms and was not taking any medications. She had no history of past illnesses, trauma, operations, or hospitalizations. Because of a positive family history of diabetes, she had been having her blood glucose monitored yearly for the previous 5 years. A fasting plasma glucose (FPG) concentration had been 5.4 mmol/L (97 mg/dL) 9 months earlier.

On ophthalmologic examination, there was no perceptible ptosis and no iris heterochromia. There was a 2-mm anisocoria in room light with the smaller right pupil manifesting a dilation lag in dim illumination. There was no evidence of cataract or retinopathy. There was no appreciable anhidrosis. There was a reversal of baseline anisocoria 60 minutes after bilateral conjunctival instillation of 1 drop of 0.5% apraclonidine solution, with the right pupil becoming 1 mm larger than the left pupil. Results of the neurologic examination were otherwise normal.

The FPG concentration was 10.5 mmol/L (189 mg/dL), triglyceride concentration was 2.8 mmol/L (248 mg/dL), and low-density lipoprotein (LDL) cholesterol concentration was 3.1 mmol/L (120 mg/dL). Repeat FPG concentration was 9.9 mmol/L (178 mg/dL) with hemoglobin (Hb) A1c of 7.3%. Serum creatinine and urinary microalbumin concentrations were within normal limits. Results of VDRL, fluorescent treponemal antibody (FTA) absorption, and tuberculin test were all negative. MRI of the head, neck, and thorax as well as ultrasonography of the neck and mammography of both breasts, did not reveal any pathologic conditions.

A diagnosis of type 2 diabetes with a right “Horner pupil” was made. She was prescribed 1000 mg metformin twice daily and was advised to lose weight through dieting and exercise.

Three months later, she had lost 10 kg; her FPG concentration was 4.9 mmol/L (89 mg/dL) and her HbA1c and lipid profile were normal. The pupils were equal in size with normal reactions to light and a near target. Retesting with apraclonidine instillation demonstrated no anisocoria; the supersensitivity was gone.

Diabetic autonomic neuropathy causes loss of sympathetic function and is associated with increased tissue sensitivity to catecholamines. Supersensitivity to catecholamines could be due to a postsynaptic increase in sensitivity or to decreased catecholamine uptake into sympathetic nerve endings (4–6). α-Agonist-receptor interactions are coupled through the G protein complex to phospholipase C. The latter catalyzes the hydrolysis of phosphatidylinositol biphosphate (PIP2) into diacylglycerol (DAG) and inositol triphosphate (IP3). These intracellular messengers, in turn, activate further specific enzymes, culminating in catecholamine action. Also the interaction of the α protein with the receptor affects the affinity with which the receptor binds its ligand. Moreover, the effect on binding affinity depends on whether guanosine diphosphate (GDP) or guanosine triphosphate (GTP) is bound to the G protein. In diabetes, there may be a supersensitivity to α-agonists, probably owing to high activity of phospholipase C (with an increase in DAG production), which induces alterations in the membrane α-adrenergic receptors (5).

Topical apraclonidine is used for reduction of intraocular pressure in acute angle closure glaucoma and after
ytrium-aluminum-garnet (YAG) laser therapy (7–9). In this regard, the major site of pharmacologic action of apraclonidine for reduction of aqueous production is the postjunctional α2-receptors in the ciliary body. The drug also has a weak α1-adrenergic effect. In Horner syndrome, sympathetic denervation induces an up-regulation of α2-receptors (4–6), which also unmask the α1 effect of apraclonidine, clinically causing pupil dilation. Apraclonidine is thus a useful medication to confirm the clinical diagnosis of Horner syndrome regardless of the site of the lesion (7–9).

Anisocoria with supersensitivity to topical apraclonidine has not been reported as an initial sign of diabetes mellitus that disappears with appropriate regulation of blood glucose. This patient is a reminder that, particularly when ipsilateral ptosis is absent, diabetic pupillary autonomic neuropathy should be considered as a cause of these phenomena before one embarks on an imaging investigation of mass lesions in the sympathetic pathway.

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Nonarteritic Ischemic Optic Neuropathy After LASIK With Femtosecond Laser Flap Creation

Non-arteritic ischemic optic neuropathy (NAION) has been reported after laser in situ keratomileusis (LASIK) performed with a microkeratome flap (1,2). Its occurrence has been attributed to the pressure elevation caused by the suction ring. The suction ring placed during hyperopic LASIK transiently elevates the intraocular pressure (IOP) to levels exceeding 65 mm Hg.

We examined a 53-year-old man who developed unilateral NAION after bilateral simultaneous uncomplicated hyperopic LASIK in which flap creation was performed using the IntraLase femtosecond laser (IntraLase Corp., Irvine, CA) with a low-pressure suction ring. To the best of our knowledge, NAION has not been reported in this setting.

Preoperative refractive errors were +5.50 +0.50 ×105 for the right eye and +5.25 +0.50 ×90 for the left eye with best-corrected visual acuities of 20/20 in both eyes. Preoperatively, IOPs were normal and family history was negative for glaucoma. The LASIK surgeon reported that results of a preoperative dilated fundus examination was unremarkable except for small optic discs and cup/disc ratios.

The procedure was uneventful. In each eye, the IntraLase femtosecond laser was used to create superiorly hinged flaps of 110 μm thickness, and stromal ablation was performed. Corneal topography after LASIK surgery revealed a hyperopic LASIK ablation pattern.

On the first postoperative day, best-corrected visual acuities were 20/20 in the right eye and 20/200 in the left eye. The right optic disc was normal, and the left optic disc was edematous. There was a relative afferent pupillary defect in the left eye. Visual field examination showed a dense nerve fiber bundle defect in the left eye (Fig. 1).

In the two reported cases of NAION after LASIK surgery (1,2), flap creation was performed using a mechanical microkeratome, with an associated sudden increase in IOP to 60–70 mm Hg, followed by a rapid IOP decrease upon suction release. Our patient is unusual because during IntraLase laser treatment, the IOP did not exceed 30–40 mm Hg (3,4). The mechanism of NAION under these circumstances is unknown.
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**FIG. 1.** On postoperative day 1 after bilateral hyperopic LASIK procedures with femtosecond flap creation, fundus photographs (A) show left segmental optic disc edema, and visual fields (B) show a corresponding left eye defect.
Notice: Duplicate Publication

We would like to provide an explanation for the fact that our publication entitled “Wall-eyed bilateral internuclear ophthalmoplegia in a patient with progressive supranuclear palsy” published in the June 2008 issue of the Journal (1) involved the same patient as reported in another publication from our institution entitled “Progressive supranuclear palsy with wall-eyed bilateral internuclear ophthalmoplegia syndrome” (2).

We have written our paper independently, basing it mainly on the findings on electroneystagmography and vestibular testing. We did not know that Dr. Matsumoto and his colleagues were going to publish the case report about the same patient. We had no intention of duplicate publication. Insufficient communication between us and Matsumoto and co-authors has brought about this matter.

We have already reported the error to our institution. We are consulting with experts in our institution to develop an institutional means to prevent recurrence of this sort of mistake. We will propose new effective rules for publication in our institution.

We apologize for this matter caused by our insufficient communication.

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REFERENCES

Reply:
The Journal of Neuro-Ophthalmology accepts the apology of Drs. Ushio et al. for having unknowingly submitted for publication to this journal a case report prepared concurrently by other authors for publication in another journal.

It is acceptable to present the same case material in more than one publication if it is not the principal focus of the articles and the interpretation of the findings is very different. Otherwise it is either a serious breach of ethics or a serious example of sloppiness.

With the growth and increasing complexity of academic medical centers, this kind of mistake is bound to happen—and it happens often. The editorial staff of medical journals has no way to prevent it. The burden is on the investigators and their host institutions to develop a reliable communication system.

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Neuroscience: Fundamentals for Rehabilitation, 3rd Edition

Scope: In covering the fundamentals of the normal and abnormal nervous system in humans, from the basics of anatomy to disease states that affect the central and peripheral nervous systems, this book seems to be primarily intended for the beginning practitioner. Authored almost entirely by Dr. Lundy-Ekman, it is a practical reference for practitioners with limited interaction with this patient population. This 575-page highly illustrated textbook also includes an additional 16-page glossy atlas of the brain and a CD-ROM with 40 illustrative animations/videos.

Strengths: This textbook is clearly and accurately written in a simple and easily understood style. The text is divided into sections and subject headings that make reading pleasurable. There are ample tables, illustrations, photographs, and clinical examples to expand on the text. The linkage between the neuroscience and clinical fundamentals is excellent.

Weakness: The content of this textbook is too superficial to serve as a "go-to" reference for the mid-level or experienced practitioner. The neuroscience background material is interesting and well written but inadequate for the textbook to serve as a resource text. The accompanying CD-ROM offers little practical information and does little to truly augment the textbook.

Recommended Audience: This textbook, although pleasant to read and review, has a narrow clinical audience. It does not offer enough depth to serve a role for the basic neuroscientist. It should serve, however, as a good introductory text for allied health professionals, including nurses.

Critical Appraisal: Although eye-catching and well written, this text has limited depth of clinical information, which prevents it from being a "must have" resource for physicians in the field of neuroscience. Unfortunately, this same limitation prevents it from serving a particular role as a resource for practitioners who only see occasional patients with disorders of the nervous system.

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Scope: Neuroanatomy books tend to focus either on verbal descriptions or on visual presentations. This book clearly falls into the latter category. It is a true atlas, with far more space devoted to pictures than to words. Although several sections do contain accompanying (and welcome) text, the stars of this book are the pictures.

The book is divided into five parts. The first part is primarily a textual introduction. It is worth the small time investment to read as it sets the stage for the rest of the book. It is also packed with interesting trivia you either never learned, or if you did, you have certainly forgotten. For example, do you remember that the brain contains about 100 million neurons?

The second part is entitled “The CNS and Its Blood Vessels.” Diagrams, photographs, embellished photographs, and angiograms provide an effective summary of how blood is delivered and recovered from the brain, brainstem, and spinal cord.

The third section, “Brain Slices,” provides a classic overview of neuroanatomy. The pictures are excellent. Unlike some neuroanatomy atlases, labels of named structures are placed directly on the photographs of the brain slices. This is quite welcome, as atlases that require the eyes to jump back and forth require substantially more time to digest. Labeled brain slices are presented next to corresponding MRI images, which are also labeled. I found this section refreshingly practical and efficient.

Part 4 is entitled “Histological Sections.” It provides enlarged, stain-enhanced photographs of critical brain regions. It nicely complements the more general photographs and radiographs from part 3.

Part 5, called “Pathways,” delivers more than information on neuroanatomical connections. It is organized by structure, with the detailed anatomy of the specific structure under consideration, its anatomic relation to neighboring and associated structures, and its efferent and afferent connections presented in direct progression. In some instances, these pathway overviews are the clearest, most concise, and easiest to digest that I have ever come across. The reader can quickly walk away with a nice review, or if deeper knowledge is desired, it, too, can be extracted.
**Strengths:** The figures are very clearly labeled, and neuroanatomical pathways are nicely laid out. This edition has more magnetic resonance images than the previous one. It is wonderful to have a portable, easy-to-use reference that allows you to simultaneously review an actual brain dissection and its corresponding MRI cut. The focused treatments of particular brain regions and systems included in the final sections are excellent.

**Weaknesses:** Some sections would benefit from a bit more text explanation. For example, in the thalamus the usual ventral-dorsal conventions do not apply, a fact that is not discussed. Avoiding some of the more common eponyms may leave the reader wanting. For example, there is no mention of the Papez circuit, which is perhaps unusual for a neuroanatomy atlas or text.

**Recommended Audience:** This book is recommended for anyone studying human brain anatomy. Because it is so concise and clear, it will suit students from multiple levels or disciplines (undergraduate, graduate, medical, and physical therapy). Neuroscientists from disciplines in which neuroanatomical knowledge is requisite will appreciate this book. This book will also benefit physicians requiring advanced knowledge of the human nervous system (neurologists, neurosurgeons, neuro-ophthalmologists, and psychiatrists). Physicians at the resident level trying to learn neuroanatomy will find this book extremely useful. Post-residency physicians preparing for recertification examinations or those who want to efficiently refresh their fading neuroanatomical knowledge will love this book.

**Critical Appraisal:** This book is designed to provide a visual overview of human neuroanatomy. It succeeds admirably. For those hoping to master the subject matter, it will prove to be a valuable adjunct to neuroanatomy books that focus more on text and less on images. Those already familiar with the subject but who could benefit from a review of neuroanatomy will benefit enormously. I did.

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**Specialist Training in Neurology**


**Scope:** This is a 319-page multiauthored paperback book describing the basics of clinical neurology for the neurologist in training. The chapters highlight the fundamentals of the neurologic examination, anatomical localization, and common neurologic diagnosis and management. There is also a concise chapter covering the most common neuro-ophthalmologic signs and symptoms.

**Strengths:** Each chapter begins with a brief clinical case highlighting the chapter topic. The information is organized in a concise and readable format (bullet points, text boxes, and diagrams), allowing busy interns or residents to continue basic self-directed learning of clinical neurology. In addition, each chapter is short enough to be read in one sitting. There are many MRI brain and head CT scans that correspond to the topic at hand. In addition, two of the greatest strengths of the text are the numerous well-illustrated color diagrams of basic neuroanatomy and color-coded tables highlighting clinical features and differential diagnosis.

**Weakness:** As a review text, this book serves as a supplement to a more complete clinical neurology reference text. Apart from the first two chapters (the neurologic consultation and basics of neuroanatomy), there is no specific organization to the order of the chapters or the material within each chapter.

**Recommended Audience:** This book is most appropriate for first-year neurology residents. Medical students or interns planning to specialize in neurology, ophthalmologists, and other physicians will find this to be a readable text for reviewing clinically relevant neurology.

**Critical Appraisal:** This is a well-illustrated review book of clinical neurology and would serve as a good supplement to a comprehensive neurology textbook.

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The Future of the Brain: The Promise and Perils of Tomorrow’s Neuroscience


**Scope:** As the title indicates and the first chapter summarizes, this single-authored text is about the current state of brain neuroscience and its application to perceived social and medical disorders. The text is written primarily for a lay audience with a good college-level or higher background in the biologic sciences. The first seven chapters review the evolution of brains, the development of the
modern mammalian brain, including epigenetic influences, and the mature brain’s organization and senescence. There are several informative illustrations in these chapters. The last five chapters build upon this background and present the arguments for hope, but primarily for caution, in the application of neuroscientific findings to social maladies and medical disorders ranging from neurodegenerative to psychiatric and the uncertain territories between them.

**Strengths:** To review the biologic history of the brain from the origin of life to senescence is a daunting task, but Professor Rose, a senior neuroscientist at the Open University and a Visiting Professor at University College, London, UK, presents these complex concepts in easily readable prose. One is not likely to find elsewhere a more comprehensive review in so limited a space. The purpose of this review is to set the stage for the more polemic chapters to follow. These last four chapters are introduced by a linking chapter, Chapter 8, which discusses the limitations, imposed by our imperfect knowledge and technology, on our ability to predict the experiential and behavioral results of brain activity or of manipulating the brain. The final chapters review and critique current and possible future attempts to use electrophysiologic and neuroimaging recordings to assess private experience, and pharmacologic, surgical, or even electromagnetic interventions to manipulate brain function. Many of these issues are of serious concern now or will be in the near future.

**Weakness:** The history of the brain does not require speculations about the origin of life, and Professor Rose seems to overextend himself in this area. In dealing with the familiar nature-nurture arguments about brain evolution, development, and plasticity, the author frankly assaults views he deems excessively deterministic (Steven Pinker’s, for example) and this seems unnecessary, given the main thrust of his final arguments at the end. Some of the discussion about the possible future misapplications of neuroscientific knowledge seems exaggerated; for example, it is unlikely that “thought control” by remote electromagnetic stimulation is likely to become a public, or even, military threat any time soon.

**Recommended Audience:** Neuroscientists and physicians, especially those in the neurologic disciplines, will find this an interesting, informative, and provocative book. In addition, those in the health care “industry,” the professions dealing with medical-legal issues, and students in these fields should read this book. The wider audience of biologically knowledgeable laypersons will benefit from becoming informed about the importance and broad social impact of the neurosciences.

**Critical Appraisal:** Professor Rose has presented a review of the brain’s history that is impressive for its breadth and cogency. What it lacks in depth and detail is more than balanced by its effectiveness as an introductory background for his argument to follow. His style is highly personal so that I felt I understood his argument from the background of his experience as a teacher and neuroscientist. As part of that personal relationship, I regretted his occasional snipe at others who support what he considers a rigid, highly deterministic view of brain development and function. Having read most of the authors he cites in this regard, I think he overstates the differences. As he introduces his cautionary arguments, Professor Rose uses a clever imaginary device, the “cerebroscope,” to demonstrate that, regardless of how detailed our information about brain function may be, we are, and probably will forever be, unable to predict individual experience or behavior to the degree necessary to control human behavior or cure many of the neurologic or psychiatric diseases. There is far more about perils than promises in this book, and perhaps the promises have been so neglected as to give the impression of therapeutic nihilism. Nonetheless, anyone with a relationship to the neurosciences and their application to medical or social issues must face the problem of avoiding both hubris and inertia. Professor Rose’s book is a good place to start.

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**The Nervous System: Basic Science and Clinical Conditions**


**Scope:** This book is part of the Systems of the Body series designed primarily for medical students as a problem-based neuroscience course. The authors explain that their aim is to cover basic elements of structure and function of the nervous system and major pathologic conditions. The first part of the volume provides instruction in both the general organization of the nervous system and cellular neuroscience. Later chapters describe systems with clinical scenarios and delve into diagnosis and management issues. Each chapter begins with a half dozen clearly stated objectives and concludes with self-assessment questions. There is an answer section at the very back with full discussions of these questions.

**Strengths:** The British tone of the writing is quaint and charming. For example, an opening analogy of the nervous system to a car asks the reader to “open the bonnet and check the petrol.” The organization and writing make reading this material easy and entertaining, and the illustrations include
some clear and elegant schematic diagrams. There are also some fine examples of neuroradiologic imaging. The quality of reproduction on glossy paper is excellent. This book succeeds in combining the best of British didacticism with a modern problem-oriented style.

**Weakness:** Unfortunately, clarity sometimes comes at the cost of superficiality and even accuracy. There are misstatements and errors of fact in the text and in the figures. In Chapter 7, the reader is told that there are many serious causes of blindness requiring patients to visit their “optician”. Multiple sclerosis is described as a disease in a separate category from inflammations. The choroid is described as a brown membrane, and “pigment is produced by the melanocytes of the retinal pigment epithelium.” Figure 7.2, a classic photo of background diabetic retinopathy, is described as “hypertensive diabetic neuropathy.” Although this chapter seems particularly replete with errors, several other chapters are problematic as well.

**Recommended Audience:** Although aimed at medical students, this book will be popular among neurology residents. Neuro-ophthalmologists will be troubled by the many inaccuracies in the chapter on the visual system.

**Critical Appraisal:** This book makes clinical neuroscience very attractive. However, the multitude of sins described above mitigates its value and precludes its endorsement as a standard textbook for teaching neurology or as a scholarly reference book.

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**Neurobiology of Disease**


**Scope:** This text is a scholarly review of the pathophysiology and molecular biology of neurologic disease edited by one of the leaders of modern academic neurology, a clinical neuroscientist. Its goal is to provide information on current concepts and developments, placed in clinical context, to better define areas of opportunity for basic scientific investigation. It does not seek to be all-inclusive, but rather to focus on areas of substantial current activity or particular investigational promise. Nevertheless, it encompasses a vast spectrum of neurologic disease.

The 95 chapters are divided into 18 sections, including metabolic diseases, neurodegenerative disorders, genetic diseases, neuroimmunologic disorders, cerebrovascular diseases, paroxysmal disorders, neoplastic diseases, infectious diseases, motor neuron diseases, malformations and developmental disorders, neurologic manifestations of medical diseases, sleep disorders, substance abuse and basic toxicology, imaging and the nervous system, peripheral neuropathies, myopathies and neuromuscular junction disorders, autonomic disorders, and pain.

It is not heavily illustrated. But the illustrations provided (some in color) are generally well chosen and of very high quality.

**Strengths:** It would take extraordinary effort to track down isolated reviews on all the topics covered in this book. To have them provided for us under one cover, with the uniformity and consistency of vision achieved by a strong editor and with the able assistance of section editors, is remarkable. The chapters are generally well written and some are gems. Given the targeted audience, one might have expected much inscrutable molecular neurobiology. With only occasional exceptions, however, this is not the case, and the content of the book is very much accessible to the informed clinician.

**Weaknesses:** As in any edited text, there are some very strong chapters and some that do not excel. Some authors were at a disadvantage to start with as they strived to write chapters on disorders for which the neurobiologic basis is still poorly understood.

**Recommended Audience:** As a clinical scientist, I am not in a position to judge how well Dr. Gilman has reached his target audience. However, the goal of this text was to summarize what is known about the why’s and how’s of neurologic diseases, and it provides us much of the bounty of the revolution in molecular biology that has occurred over the past 15 years. As such, it is of potential interest to all neurologists, and most academic neurologists will find it fascinating. Although the content is probably too dense for it to become a routine component of the resident curriculum, it provides a superb guide to ways of thinking about neurologic disease that residents so need, ways of thinking that will endure even as the facts change.

**Critical Appraisal:** Many, perhaps even most, fields of neurologic research suffer from a gap that exists between basic and clinical scientists. This ambitious and successful text should help to bridge that gap. It may also help clinicians to decipher the endless enigmas that their patients continually pose.

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The 2008 International Stroke Conference was held at the Ernest N. Morial Convention Center in New Orleans, Louisiana, February 20–22, 2008 and had more than 5,000 attendees. The meeting included more than 600 oral and poster presentations. The following papers were of special interest.

**ACUTE ISCHEMIC STROKE**

1. **EPITHET**

   Intravenous tissue plasminogen activator (tPA) is currently administered to eligible patients within 3 hours of ischemic stroke onset. If an ischemic penumbra can be documented, the possibility exists for extending the time window to increase the number of patients treated. Stephen M. Davis, MD, University of Melbourne, Australia, reported the results of the Echo-Planar Imaging Thrombolysis Evaluation Trial (EPITHET) with full publication in *Lancet Neurol* (2008;7:299–309). The study is based on the hypothesis that a perfusion and diffusion MRI mismatch would signify potentially salvageable tissue. Thrombolysis might attenuate infarct growth by increased reperfusion of this area. The study was a double-blind, placebo-controlled, phase 2 study at 15 centers in Australia, New Zealand, Scotland, and Belgium. Patients who were tPA-eligible by National Institute of Neurological Disorders and Stroke criteria presenting 3–6 hours from onset of stroke symptoms underwent diffusion, perfusion, and MRA imaging. After imaging, one half of the patients received tPA and the remainder received placebo. Repeat imaging was performed at days 3–5, and T2 MRI was performed after 90 days. The primary outcome was infarct growth between baseline diffusion imaging and the day 90 T2 lesion in mismatch patients using a ratio of geometric means. A total of 101 patients were enrolled in the trial. Data were analyzed from 44 patients in the tPA group and 47 patients in the placebo group. Mismatch was defined as perfusion imaging > diffusion imaging volume by 20% and perfusion-diffusion image volume of at least 10 mL. Using this definition, 37 of 44 tPA patients and 43 of 47 placebo patients had a mismatch. The primary outcome of relative infarct volume growth was 1.24 for the tPA group and 1.78 for the placebo group (P = 0.24). The major secondary outcome was reperfusion, defined as >90% reduction between baseline and day 3 perfusion imaging volumes. This outcome significantly favored the tPA group, with 56% reduction in the tPA group and 26% reduction in the placebo group (P = 0.01; 95% CI: 9%–51%). There was no significant clinical difference in the mismatch patients who received tPA compared with those who received placebo. Four patients, all in the tPA treatment group, had symptomatic hemorrhage. Because of the small number of non-mismatch patients, the authors were unable to compare the mismatch and non-mismatch groups. The trial results support the feasibility of performing MRI in acute stroke patients, although the feasibility of processing the perfusion image acutely for real-time clinical decision-making was not addressed and represents a major limitation of this work. The authors concluded that EPITHET results provide biologic support for extension of the time window for tPA and the need for a larger trial. Although not conclusive, this study provides evidence that further trials examining the use of acute MRI to extend the tPA window are needed.

2. **CCHIPS**

   Blood pressure reduction is beneficial for primary and secondary stroke prevention. The management of hypertension in the setting of acute stroke is unclear. John Potter, MD, University of East Anglia, United Kingdom, presented data from the Control of Hypertension and Hypotension Immediately Post-Stroke (CHIPS) pilot trial. CHIPS is a multicenter, prospective, randomized, double-blind, placebo-controlled titrated dose phase 2 trial in the United Kingdom. Patients aged older than 18 years without recent antihypertensive treatment who have systolic blood pressure (SBP) greater than 160 mmHg were randomized within 24 hours and, later in the study, up to 36 hours after onset of their suspected stroke symptoms. Patients undergoing thrombolysis were excluded. Patients were randomized to oral medications of 50 mg labetalol or 5 mg lisinopril or placebo if they were able to swallow. Patients who were unable to swallow were given sublingual lisinopril, intravenous labetalol or placebo. The blood
pressure readings were repeated at 4 and 8 hours and, if the target systolic blood pressure of 145–155 mm Hg or a 15 mm Hg fall in blood pressure was not achieved, the antihypertensive medication was repeated. The titrated dose was continued for 14 days. In the dysphagic group, the medications were administered by nasogastric or gastrostomy tube.

A total of 179 patients were randomized (58 patients to the labetalol group, 58 to the lisinopril group, and 63 to the placebo group). Nearly half of each group was composed of dysphagic patients. The study included patients with ischemic and hemorrhagic strokes. Patients undergoing thrombolysis were excluded. The mean National Institutes of Health Stroke Scale (NIHSS) score was 11. The primary outcome was the proportion of patients dead or dependent (dependence defined as a modified Rankin Scale score > 3 at poststroke day 14). There was no difference between the active treatment group and the placebo group regarding the primary outcome of death and dependence at 14 days (odds ratio: 1.08; 95% CI: 0.55–2.03). Lowering blood pressure did not have an adverse effect on neurologic status, defined as increase in NIHSS ≥ 4 or death at 72 hours (antihypertensive drug 7% vs placebo 10%, P = 0.56).

The major strengths of this study were the use of a clinical end point and the ease of the treatment protocol. Blood pressure reduction did not alter death or disability at 2 weeks, and it was not associated with deterioration of neurologic status at 72 hours. The authors concluded that a large trial is needed to confirm these results.

INTRACEREBRAL HEMORRHAGE

1. Subanalysis of FAST Trial

During the first 3 hours after intracerebral hemorrhage (ICH), hematoma expansion is common and associated with a worse outcome. In the phase 2b trial of the Factor Seven for Acute Hemorrhagic Stroke Treatment (FAST) trial, a dose-related reduction in mean percentage change in ICH volume at 24 hours was shown in patients treated with recombinant activated factor VII (rFVIIa). The phase 3 FAST trial randomized acute intracerebral hemorrhage patients to receive 80 μg/kg or 20 μg/kg of rFVIIa or placebo. The primary outcome was death or severe disability, defined as a 90-day modified Rankin Scale score of 5 or 6. There was no significant difference in severe disability or mortality between the placebo and rFVIIa-treated groups. However, there was a significant decrease in mean percent change in hematoma growth measured at baseline and at 24 hours in the patients who were treated with 80 μg/kg of rFVIIa (11%) compared with the placebo patients (26%, P = 0.0004). Stephan Mayer, MD, Columbia University, New York, presented the results of a subgroup analysis of patients treated with 80 μg/kg rFVIIa compared with placebo. The data were examined continuously and then combined into various clinically feasible groups to identify an optimal subgroup. The data from this group were then evaluated in the phase 2 trial.

The optimized target population was found to be patients aged younger than 70 years who were treated within 150 minutes and who had less than 5 mL of intraventricular hemorrhage (IVH) volume and less than 60 mL of ICH volume. The odds ratio of death or disability for all patients treated with 80 μg/kg rFVIIa in the phase 3 trial was 1.39 compared with 0.28 for the optimized group, a result that was not significant. The authors proposed a clinical trial with rFVIIa for ICH in this optimized patient population.

It was disappointing that the phase 3 FAST trial did not demonstrate clinical efficacy after the promising results of the phase 2b trial. Whether rFVIIa will be a clinically useful treatment for acute ICH remains doubtful.

2. INTERACT

Elevated blood pressure after ICH is common, and the optimal management strategy has not been established in a large clinical trial. Such a strategy likely would need to strike a balance between presumed reduction in infarct growth from persistent hypertension and maintenance of cerebral perfusion to prevent extension of brain injury. Craig Anderson, MD, University of Sydney, Australia, presented the results of the first phase of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT). This vanguard (pilot) phase was intended to gather feasibility and recruitment capacity data. It also examined hematoma expansion, an important surrogate end point. Patients were eligible if they had a CT-confirmed ICH and elevated SBP between 150 and 220 mm Hg. Subjects were randomized to intensive treatment (target SBP of 140 mmHg within 6 hours) or current standard treatment (American Stroke Association guideline target SBP of 180 mmHg). As this was an international trial, the investigators at each site could choose different blood pressure–lowering agents. The trial hypothesis was that the intensity of blood pressure lowering and not the choice of a specific agent would drive the clinical effect. The primary outcome measure was proportional hematoma volume growth at 24 hours using digital analysis of CT images. The safety of the treatment strategy was assessed by measuring clinical outcome at 90 days.

Centers from Australia, China, and Korea enrolled 404 patients in this pilot trial between November 2005 and April 2007. About 95% of the total enrolled patients were from China. Baseline characteristics of the treatment and control groups were similar. The SBP was 13.3 mm Hg lower in the treatment group at 1 hour and 10.8 mm Hg lower during hours 1–24 (P < 0.0001 for comparison.
between treatment and control groups at both time periods). The primary outcome, mean proportional hematoma growth, was 13.7% in the treatment group versus 36.3% in the control group with an absolute difference of 22.6% (95% CI: 0.6%–44.6%). The total hematoma volume in the control group was 12.7 mL at baseline and 15.4 mL at 24 hours. In the treatment group, the hematoma volume was 14.2 mL at baseline and 15.2 mL at 24 hours. No significant differences between the treatment and control groups were observed for clinical or safety outcomes. Case fatality was 10% in the treatment group and 12% in the control group. The authors concluded that the larger phase of this trial powered to determine efficacy for a clinical outcome should go forward. The safety of this strategy appears sound.

It is somewhat disappointing that a larger clinical effect on patient outcome was not observed, but this pilot study was not designed to detect this. Of additional concern is the generalizability of the results, given that most enrolled patients were from China and that hematomas were relatively small in volume. The small volumes observed were concordant with the authors' observation that the mild clinical status of the patients in this trial was an important limitation, and probably tended to decrease the ability to detect clinical outcome differences. The larger hematoma volumes at baseline in the treatment group probably also contributed to this. The recruitment strategy appeared to be effective, but enrollment of a less heterogeneous population for the main phase of this trial will be crucial.

STROKE EPIDEMIOLOGY

1. Daytime Sleepiness

A growing body of evidence suggests that sleep plays a crucial role in cardiovascular risk. In stroke, this relationship has been examined with respect to disordered sleep, but prospective population-based studies have been limited. Bernadette Boden-Albala, MPH, DrPH, Columbia University, presented findings from the Northern Manhattan Study (NOMAS), a population-based prospective cohort study. The goal of the investigators was to explore the relationship between daytime sleepiness and the risk of stroke and other cardiovascular events. Daytime sleepiness was chosen as it was believed to be a good surrogate marker for disordered sleep, an important risk factor for cardiac disease, hypertension, and stroke. Subjects in the study had assessment of the Epworth Sleepiness Scale (ESS) or the number of days in a week spent snoring and amount of choking during sleep. The patients were then followed for the occurrence of vascular events; analysis was performed by Cox proportional hazard ratio estimation.

Nearly 2,000 subjects were followed for a mean of 2.3 years. There were 156 deaths, 123 vascular events, and 40 strokes. The cohort had a mean age of 73 years and was 64% female and approximately 60% Hispanic (remainder split between whites and blacks); 72% were hypertensive; diabetes and coronary artery disease were each seen in approximately 20%. Of the subjects in the cohort, 44% reported "no dozing" (ESS = 0), 47% reported "some dozing" (ESS of 1–9), and 9% reported "significant dozing" (ESS of 9 or above). After adjustment for stroke risk factors, the hazard ratio for "some dozing" (with "no dozing" as reference class) was 2.6 (95% CI: 1.1–6) and for "significant dozing" was 4.5 (95% CI: 1.5–13). The investigators concluded that further studies of the relationship between stroke and sleep are needed.

Although preliminary, this work has probably established daytime sleepiness as a novel risk factor for stroke. These results are impressive in that a simple and easy-to-administer scale (the ESS) was used to define the risk factor. The high hazard ratios reported, along with the dose-response relationship, are additional strengths of this work. The cohort, as evidenced by a high burden of stroke risk factors at baseline, is not reflective of the overall population. Extension of this work to a wider population of subjects at risk for stroke will be necessary to draw broader conclusions.

2. Stroke Risk Factors Are Predictive of Cognitive Decline

The relationship between ischemic stroke, even subclinical events, and cognitive functioning is well known. The more subtle, yet very important, relationship between cardiovascular risk factors and cognitive decline has not been explored previously in a large population-based study. George Howard, DrPH, University of Alabama at Birmingham, presented the results of a study from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, a large population-based cohort study examining differences in stroke risk between white and African-American subjects. The REGARDS study also examined the contribution to disease burden of the "Stroke Belt," a geographic area of the United States with a significantly higher stroke mortality. The investigators sought to examine whether stroke risk factors predict cognitive decline. Participants in the REGARDS study are recruited community dwellers who undergo baseline interviews, physical examinations, laboratory tests, and electrocardiograms. There is central monitoring for detection of possible stroke events and cognitive decline. Cognitive function is assessed via a validated, six-item screening test derived from the Mini-Mental Status Examination (MMSE). The stroke risk factors are the components of the Framingham Stroke Risk Function: SBP, medications, diabetes, smoking, heart disease, atrial fibrillation, and left ventricular hypertrophy. Demographic, educational, and mood-related
(depression) factors were considered as possible effect modifiers.

The cohort contained approximately 30,000 subjects. Subjects who had a validated stroke or transient ischemic attack were excluded (at the point of time when the event occurred). The mean stroke risk in the cohort was about 1% per year. The estimates for annual mean change in the cognitive score were reported graphically at the conference. The baseline group (with 0% risk of stroke over 10 years according to Framingham score) had an annual decline of 0.02. The group with the highest risk (31.5% 10-year risk of stroke) had an annual cognitive decline of 0.11. The groups with average risk (10.5% 10-year risk of stroke) and elevated risk (21% 10-year risk of stroke) had annual declines of 0.05 and 0.08, respectively. This relationship was highly statistically significant ($P < 0.0001$).

The investigators have shown that the Framingham Stroke Risk Function is strongly associated with annual rate of cognitive decline. One important limitation of this study is that the clinical importance of the measurement scale for cognitive decline is unclear, especially because it was derived from the MMSE, which has limitations of its own. Even so, the results provide strong evidence that the burden of stroke risk factors probably plays an important role in cognitive decline, even in the absence of clinically apparent stroke.

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Upgrades in the Neuro-Ophthalmology Virtual Educational Library (NOVEL)

The Neuro-Ophthalmology Virtual Educational Library (NOVEL, http://library.med.utah.edu/NOVEL/), NANOS’ online repository of educational resources, has undergone some important upgrades within the past year.

Hosting Agreement. Founded in 2002 with an Information Systems grant from the National Library of Medicine, NOVEL signed a memorandum of understanding with the Eccles Health Sciences Library at the University of Utah in Spring 2007. The Eccles Library will host the site and provide technical support, but the site will remain under the direction of NANOS. Nancy Lombardo acts as project director and librarian, working closely with a NOVEL Executive Committee comprising NANOS members.

Website Redesign. A new look to the website appeared in July. It is more compatible with the NANOS website and should provide intuitive navigation to all the collections and services of the project. A new Advanced Searching feature is available now from the NOVEL home page.

Completed, Expanded, and New Collections. Three collections have been completed: The William F. Hoyt Collection of the best examples of disorders of the optic disc contains more than 850 images with descriptive metadata. These images have also been harvested into the larger Health Education Assets Library (HEAL) at http://www.healcentral.org/. The collection of historical lectures by J. Lawton Smith, MD, which were recorded in the 1970s, covers more than 80 topics. The AAO-NANOS collection holds more than 400 images contributed by more than 30 NANOS members. The collection is derived from the CD produced by Larry Frohman, MD and Andrew Lee, MD in the 1990s.

Growing collections include the visual disorder case videos of Shirley Wray, MD, PhD which has links to pathologic and radiographic findings. Dr. Wray is collaborating with Nancy Lombardo and the staff in Utah to complete her case list, editing video clips, developing teaching lectures in PowerPoint, and composing the complex and comprehensive metadata that characterize her collection.

The Walsh Society Meeting collection now contains the Walsh abstracts and discussions covering 1980, 1981, and 1986-2004. For the 2005-2007 meetings, complete presentations and supplemental materials are included. The Moran collection contains optic disc photos and videos of eye movements and presentations. Projects in progress include the enlarging pupil collection of Randy Kardon, MD, the eye movement collection of David Newman-Toker, MD, the pupil collection of Irene Loewenfeld, PhD, and the classic video collection of David Cogan, MD.

Additions to this line-up are the recent acquisitions of 65 cases of unique orbital surgery and pathology from John S. Kennerdell, MD, now available in PowerPoint format. The collection of nearly 100 PowerPoint lectures in neuro-ophthalmology by Alfredo Sadun, MD is in development. The videos of eye movements from Robert Daroff, MD will soon be available. The collections are under peer review by a committee headed by Leah Levi, MD.

Neuro-Ophthalmology Curriculum. The neuro-ophthalmology curriculum outline being developed under the leadership of Valerie Biousse, MD and Victoria Pelak, MD, will serve as the overarching organizational structure for all NOVEL collections. Eventually it will provide query links for retrieving materials from the NOVEL collections. This committee will be using an online mechanism to receive submissions and conduct reviews.

Patient Portal. NOVEL has received an unrestricted grant from Pfizer to develop a patient portal to access material with the aim of educating the public. Under the direction of Luis Mejico, MD, the site is based on the patient brochures written by NANOS members. There are links to reliable and authoritative information for consumers though Medline PLUS and scholarly publications from PubMed. The patient portal will also link information seekers to support groups, information within the NOVEL library, and vetted information through web resources.

Rare Disease Stewardship Program. Creating a rare disease stewardship program is another goal of the Pfizer-funded project. Stewards have been identified for rare diseases, and standardized data collection tools will be developed. The steward will be responsible for systematically collecting and organizing this information. The objective is to allow NANOS members and other interested physicians to contribute cases to the appropriate data steward, who will analyze the data. The goal is to allow NOVEL to be a vehicle facilitating group definition of the
natural history and best therapies of diseases too rare for any single institution to define.

The first disorders to be catalogued are Susac syndrome (Robert Egan, MD), autoimmune optic neuropathy (Larry Frohman, MD), posterior cortical atrophy (Victoria Pelak, MD), Chiari malformation mimicking pseudotumor cerebri (Michael Vaphiades, MD), genetic eye movement disorders (Thomas Bosley, MD), and sarcoid optic neuropathy (Mays El Dairi, MD).

Journal of Neuro-Ophthalmology Archives. An effort is underway to add the entire archive of the Journal of Neuro-Ophthalmology (JNO). An agreement has been reached with Lippincott Williams & Wilkins (LWW) to transfer the complete collection of JNO archives to NOVEL. Once transferred from LWW, the articles will be catalogued as a new collection. Articles from each new JNO issue will be added as they are released from the 1-year publisher’s access embargo. This effort will provide an alternative means of accessing the literature convenient to NOVEL users.

All Star Grand Rounds. NANOS recently approved funding to begin the production of Neuro-Ophthalmology All Star Grand Rounds. This program will make neuro-ophthalmology education accessible to residents, fellows, and practicing neurologists and ophthalmologists worldwide. The topics will be based on the NANOS curriculum and incorporate material from NOVEL.

The modules will include an audiovisual webcast lecture (showing the speakers and their PowerPoint presentation), the written material with references and weblinks (online or in printable format), and a pre/post module learning assessment that incorporates interactive case vignettes. These mini-courses will be taught by renowned experts with extensive use of video.

In the past year, NOVEL recorded over 2 million “hits” and almost 700,000 page views. There were more than 10,000 unique individual users from more than 100 countries each month.

Kathleen Digre, MD
Nancy Lombardo, MLS
Salt Lake City, Utah

Larry Frohman, MD
Newark, New Jersey

Deborah Friedman, MD
Rochester, New York
Orlando, Florida was the gathering place for the 34th Annual Meeting of the North American Neuro-Ophthalmology Society (NANOS) from March 8 to 13, 2008. The 342 attendees included 46 from outside North America (Israel, 12; Switzerland, 6; France, 5; United Kingdom, 4; Brazil, Denmark, Korea, Spain, and Venezuela, 2; Australia, Belgium, Egypt, Hungary, Mexico, and Portugal, 1). There were 23 platform presentations, 92 posters, and 3 symposia.

As usual, the program began with the all-day Frank B. Walsh Session organized by the potent Los Angeles duo of Lynn Gordon, MD, PhD and Peter Quiros, MD. Invited guests were neuropathologist David Hinton, MD, PhD and neuroradiologist Paul Kim, MD, who enlightened a rapt audience with trenchant commentary and elegant examples drawn from their teaching files.

Moderated by Valerie Biousse, MD (Atlanta, GA), and David Newman-Toker, MD, PhD (Baltimore, MD), the first NANOS symposium covered new concepts of stroke. Invited speaker Michael Frankel, MD, a neurologist specializing in stroke, delivered fine lectures on management of acute stroke and its secondary prevention. John Selhorst, MD (St. Louis, MO), and Victoria Pelak, MD (Denver, CO), put together a splendid symposium on neurodegenerative disorders. It included invited lectures by Charles Duffy, MD, James Corbett, MD delivering the first Jacobson Lecture.

Peter Quiros, MD and Lynn Gordon, MD, PhD, mouse-keteers and chairs of the Walsh Symposium.

New NANOS Candidate Members Melissa Ko, MD, Elizabeth Waller, MD, Mays El-Dairi, MD, Islam Zaydan, MD, Alice Kim, MD, and Thomas Hwang, MD, PhD.
PhD, on visual motion processing and by Henry Paulson, MD, PhD on ataxia and spinocerebellar disorders. The third symposium, organized by Nicholas Volpe, MD (Philadelphia, PA) and Michael Lee, MD (Minneapolis, MN), covered diagnostic neuroimaging. It included well-received lectures by invited speakers Matilde Inglese, MD, PhD, on imaging of multiple sclerosis and by Charles Truwit, MD, on the future of neuroimaging.

The awards for the best Walsh presentations went to Beau Bruce, MD (Atlanta, GA), and Thomas Hwang, MD, PhD (San Francisco, CA). Among the NANOS presenters, the award for the outstanding fellow’s work went to Thomas Hwang, MD, PhD. Among the resident presenters, the winner was Sashank Prasad, MD (Philadelphia, PA), and among the medical students, it was Matt Schlenker, MD (Toronto, ON). Deborah Grzybowski, MD, PhD (Columbus, OH) received the 2007 NANOS Pilot Grant Award and Kenneth Shindler, MD (Philadelphia, PA) received the 2008 Young Investigator Award. Arun Sundaram, PhD (Toronto, ON) received the NANOS/Fight for Sight Post-doctoral Fellowship Award. Kathleen Digre, MD (Salt Lake City, UT) received the 2008 NANOS Distinguished Service Award.

Joel S. Glaser, MD (Miami, FL) was recognized as the 2007 Hoyt Lecturer at the annual meeting of the American Academy of Ophthalmology in November 2007. (Dr. Glaser’s lecture appeared in the June issue of the Journal.) James Corbett, MD delivered the first Jacobson Lecture, which will be given annually at the NANOS meeting in recognition of the contributions of Daniel M. Jacobson, MD, to this specialty. (Dr. Corbett’s lecture will appear in the December 2008 issue of the Journal.

The next (35th) NANOS meeting will take place at the Hyatt Regency Tahoe Resort, Lake Tahoe, Nevada, February 21–26, 2008. For details, go to the NANOS Web site www.nanosweb.org.

Jonathan D. Trobe, MD
Ann Arbor, Michigan
Tour of posters billboard previewing the virtuosic young Nancy Newman on the left, and on the right, older brother Steven playing the cello and being pestered by very young sister Nancy.

The inner circle of NANOS officers: Anthony Arnold, MD, Ralph Sawyer, MD, Deborah Friedman, MD, Preston Calvert, MD, and Larry Frohman, MD.

Candy Chan, MD and Deborah Friedman, MD.

Valerie Purvin, MD and Kara Warden, MD.
Randy Kardon, MD and Jacqueline Leavitt, MD.

Sharon Johnstone, MD and Rosa Tang, MD.

Renee van Stavern, MD, Gregory van Stavern, MD, and Eric Eggenberger, DO.

Beau Bruce, MD and Thomas Hwang, MD, PhD, recipients of the Walsh Best Paper Award.

Thomas Carlow, MD, James Goodwin, MD, and Hazem Samy, MD.
New NANOS Fellows (left to right): Bradley Katz, MD, PhD, Nathaniel Carter, MD, Edward Kong, MD, Howard Krauss, MD, David Newman-Toker, MD, PhD, and Robert Saul, MD.

Sachin Kedar, MD, Yanjun Chen, MD, Candy Chan, MD, PhD, Sandeep Randhawa, MD, and Valerie El Malem, MD, recipients of the NANOS Resident Travel Scholarship Awards.

Deborah Friedman, MD (left) and Agnes Wong, MD, PhD, with Kenneth Shindler, recipient of NANOS 2008 Young Investigator Award.

New NANOS Fellows (left to right): Bradley Katz, MD, PhD, Nathaniel Carter, MD, Edward Kong, MD, Howard Krauss, MD, David Newman-Toker, MD, PhD, and Robert Saul, MD.
Stephen Edward Smith (1929–2007)

Stephen Edward Smith, a noted ophthalmologist and pharmacologist, died in London in December, 2007 at the age of 78. Stephen was a remarkable man whose generosity and humanity earned him a place in the hearts as well as minds of everyone who knew him. Blessed with a sharp mind and educated at Christ Church Cathedral School and later Westminster School, he won a scholarship to Christ Church Oxford to read Medicine. The clinical years of his medical training were spent at St. Thomas’ Hospital, London where he met his first wife, Marjorie, and made many friends.

After house jobs, he started his clinical career in anesthesiology, but after serving his National Service in Colchester, he decided to pursue academic medicine and applied for a research post with Professor Sam Stacey in the Department of Pharmacology at St. Thomas’ Hospital. Within 3 years, he had taken a PhD and was appointed lecturer and later senior lecturer in that department, eventually being offered a personal Chair. He developed a life-long interest in oculopharmacology, a subject then only in its infancy. Together with his second wife, Shirley, he established a pupillometry laboratory to investigate drug actions and autonomic function within the eye, publishing many papers under the now famous trademark “Smith & Smith.”

I first met Stephen when I was a medical student at St. Thomas’ Hospital, London, and immediately was aware that he was an exceptional teacher. As professor and head of the Department of Clinical Pharmacology, he used to take small groups of students onto the wards, pick up a drug chart at random, and discuss in minute detail the prescriptions. He would ask us what we thought might be the patient’s diagnosis, why these drugs had been prescribed, how we could monitor the effect of the drugs, and whether we could think of any alternative treatments and discuss their relative merits and drawbacks. Unlike many of his contemporaries, he encouraged us to think, to question, to challenge, and above all to treat the patient and not the disease. His energy and enthusiasm for teaching were legendary, his lectures and tutorials always oversubscribed, and his thoughtful, analytical approach to medicine an inspiration for many generations of medical students.

Many years later our paths crossed again when, as a young trainee in ophthalmology, I applied to work at the National Hospital for Neurology & Neurosurgery and found the recently retired professor still conducting pupillometry research out of a small converted broom cupboard in the Department of Neuro-ophthalmology. I was struck by his dedication to the patients, his enduring interest in the subject, and the meticulous care with which he carried out his experiments. We enjoyed a 10-year research partnership before his final illness, during which time I also discovered the vast breadth of his outside interests, including the other great love of his life—music (he played the violin, horn, and piano and sang in choirs). He also had a passion for theater, books, and the people of Burma. He was always polite and considerate and was loved by patients and colleagues alike. Selfless to the end, he agreed to be interviewed and photographed just before his death by the national press in support of an article about the important work done for the terminally ill by hospices (The Times: November 30th, 2007). He leaves behind two children, Alex and Simon, to whom he was utterly devoted.

Fion Bremner, PhD, FRCOphth
London, England

Stephen Smith at age 78 outside All Saints Church in Tudeley, UK, 2007.
Upcoming Meetings

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

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

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

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

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

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

46th Annual Meeting of the Japanese Neuro-Ophthalmology Society
Niigata, Japan
Contact: Dr. Mineo Takagi at 2008shinkei@shinsen.biz

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

Nov. 15–Nov. 19, 2008
38th Annual Meeting of the Society for Neuroscience
Washington, DC
http://www.sfn.org/am2008/
Contact: info@sfn.org

32nd Annual Meeting of the American Society of Neuroimaging
Orlando, FL
http://asweb.org
Contact: asn@llmsi.com

Feb. 18–Feb. 20, 2009
International Stroke Conference
San Diego, CA
http://strokeconference.americanheart.org
Contact: strokeconference@heart.org

Feb. 21–Feb. 26, 2009
Lake Tahoe, CA
http://www.nanosweb.org/meetings/index.htm
Contact: info@nansoweb.org

April 17–April 21, 2009
35th American Association of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
San Francisco, CA
http://www.aapos.org
Contact: aapos@aao.org

May 2–May 7, 2009
77th American Association of Neurological Surgeons (AANS) Annual Meeting
Chicago, IL
Contact: info@aans.org
May 3–May 7, 2009
Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Ft. Lauderdale, FL
http://www.arvo.org
Contact: arvo@arvo.org

May 16–May 19, 2009
Society of Neurological Surgeons Annual Meeting
Salt Lake City, UT
http://www.societyns.org/meeting_info.html
Contact: burchiek@ohsu.edu

May 16–May 21, 2009
47th Annual Meeting of the American Society of Neuroradiology (ASNR)
Vancouver, BC
Contact: meetings@asnr.org

May 26–May 29, 2009
XVIII European Stroke Conference
Stockholm, Sweden
http://www.eurostroke.org/
Contact: hennerici@eurostroke.eu

June 9–June 12, 2009
Canadian Neurological Sciences Federation 44th Annual Congress
Halifax, Nova Scotia
http://www.cnsfederation.org/general_information_congress.html
Contact: jroy@advance-group.com

June 17–June 20, 2009
9th European Neuro-Ophthalmology Society Meeting
Lubeck, Germany
http://www.eunos2009.org/
Contact: detlef.koempf@neuro.uni-luebeck.de

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

June 20–June 24, 2009
Canadian Ophthalmological Society Annual Meeting
Toronto, ON
http://www.eyesite.ca/english/calendar.htm
Contact: cos@eyesite.ca

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

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

Joint Meeting of the 29th Pan-American Congress of Ophthalmology
113th Annual Meeting of the American Academy of Ophthalmology
San Francisco, CA
http://www.paao.org/congress.html
Contact: info@paao.org

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