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Increased Intracranial Pressure: Idiopathic and Otherwise

James J. Corbett, MD

In this issue of the Journal, Friedman and Jacobson (1) review what we know about idiopathic intracranial hypertension. Their report is complemented by Garton's authoritative review (2) of surgical treatments of intracranial hypertension. There is also a report by Barkana et al (3) dealing with the vexing problem of intracranial hypertension, papilledema, and abnormal cells in the cerebrospinal fluid (CSF).

Now that magnetic resonance imaging and magnetic resonance venography are available, we no longer need to believe the old saw, born in the past era of angiography and pneumoencephalography, that "the commonest cause of pseudotumor is tumor." But it is still our task to be sure that patients presenting with symptoms and signs of increased intracranial pressure have no tumor, venous occlusion, hydrocephalus, or CSF cellular response.

We continue to investigate and report these patients without precise nomenclature. Clearly, there are underlying medical conditions or exogenous substances that predispose to the development of increased intracranial pressure even though we do not always understand the pathophysiology. When the condition or substance is treated or removed, intracranial pressure becomes normal and papilledema disappears. Such conditions do not necessarily favor obese women of child-bearing age. Patients with these conditions can be said to have intracranial hypertension presumed to be caused by vitamin A overdose, use of other retinoids, minocycline, lithium, or other agents.

On the other hand, there is a condition that elevates CSF pressure without clear cause eight to nine times more commonly in adult women than in men, in children with equal gender predilection, and is related to obesity (90% of women, 60% of men, and 30% of children are obese) (4-6). These patients have papilledema, headache, normal magnetic resonance imaging, and normal spinal fluid contents. This condition should be known as idiopathic intracranial hypertension (IIH).

Thus, there are patients with intracranial hypertension due to some clear predisposing cause and there are patients whose condition is idiopathic. Gone should be the days of lumping these conditions together and calling them all "benign intracranial hypertension" (BIH; it is not visually benign), "pseudotumor cerebri," or "pseudotumor syndrome." However euphonious the name "pseudotumor cerebri" or the initials BIH may be, the terms do not differentiate intracranial pressure syndromes with known cause from those without known cause.

For a long time, it was believed that the fatter you were, the higher your CSF pressure would be. Studies have shown that to be a myth (7,8). In one study of CSF pressure in obese patients and patients of normal weight without clinical features of intracranial hypertension, the most obese patients had intracranial pressures ranging between 120 and 160 mm H2O (7). All lumbar punctures performed in that study were performed by two investigators with careful attention to keeping the patient's head neutral and legs passively extended after the needle was in place. There is a tendency for physicians performing lumbar punctures to keep
the patient rolled up tight with head flexed on the chest and knees drawn into the abdomen. This practice predisposes to high cephalic venous pressure and subsequent high CSF pressure due to the involuntary Valsalva maneuver, compression of the jugular veins, and hypoventilation with CO₂ retention. These effects are likely to be more profound in obese patients and to artificially elevate CSF pressure. If patients are allowed to hold the head and neck neither flexed nor extended and legs extended, CSF pressure readings should be within the normal range. Obese and overweight patients with normal magnetic resonance venography have CSF pressures comparable to persons of normal weight (7,8). Shortly before his untimely death, Daniel Jacobson had been investigating the effect on CSF pressure when measured in the lateral decubitus position versus the prone position in fluoroscopically guided lumbar puncture. He found no difference in these two pressure measurements. More work needs to be done on establishing the normal range of measurements of CSF pressure, especially in children, for whom authoritative normative data have yet to be reported. Given that normative blood pressure values have been recently reassessed, it is reasonable to revisit what constitutes normal CSF pressure.

The issue of CSF pressure measurement and intracranial hypertension also bears on the issue of IIH without papilledema. There are certainly cases of prolonged increased intracranial pressure with unilateral or asymmetric papilledema. Increased intracranial pressure without papilledema in either eye is also well reported but is simply a headache problem, with no risk to the optic nerves. In the reports of relief of headache by acetazolamide treatment in IIH without papilledema, one wonders if acetazolamide actually could also be working as a migraine prophylactic in the manner of topiramate.

Among the more difficult issues in the clinical study of IIH is the lack of a noninvasive device to measure CSF pressure either intermittently or continuously. Currently used intracranial monitors (subarachnoid, intraparenchymal, or intraventricular) and lumbar drains, which allow continuous CSF pressure measurements, can only be used when patients are in a bed or chair, upright, or recumbent. This hardly mimics normal conditions, in which we move around in a fully upright posture. The longer these invasive devices are kept in place, the higher the risk of infection. Indirect methods of measuring intracranial pressure are being investigated (9). Some methods measure changes in tympanic membrane displacement; others measure skull deformation. They provide indirect measures of intracranial pressure, but they are not widely used and have many of the same problems that invasive devices have. They require a lumbar puncture to set the baseline pressure, and are not yet miniaturized or durable enough to make them practical in a ambulatory setting.

There are fundamentals that we still do not know about IIH. For example, we do not know when the intracranial pressure begins to rise or what triggers the rise. An empty sella is seen in approximately 70% of patients with IIH. It takes six months for an empty sella to develop. Thus, it stands to reason that a patient presenting with IIH and an empty sella has had the CSF pressure elevation for at least six months (10). Symptoms of increased spinal fluid pressure may appear only long after the pathologic process has been under way.

What becomes of intracranial pressure in the patient in whom papilledema disappears? Few lumbar punctures have been performed on patients who had IIH many years in the past. In 8 of 12 patients on whom I performed lumbar puncture up to 41 years after their clinical bout of IIH, the CSF pressure continued to be elevated even though the papilledema had resolved (4). Does axoplasmic flow somehow accommodate to the pressure differential between intravascular and intracerebral compartments after a period of time? Is this a lifelong disease? Why does papilledema clear even when increased CSF pressure continues?

Until magnetic resonance venography became available, only occasionally were attempts made to visualize the cerebral venous sinuses. One of the issues not covered in the review by Friedman and Jacobson (1) is the role of cerebral venous sinus pressure in the causation of increased intracranial pressure in IIH. Is elevated venous sinus pressure the primary cause, a contributory cause, or a secondary phenomenon? When the deep or superficial venous sinuses are occluded, the proximal end of the occluded vein (farthest from the heart) develops high pressure. This high pressure retards spinal fluid egress by increasing the pressure needed to absorb the CSF through the arachnoid (pacchionian) granulations into the venous sinuses. However, elevated CSF pressure in IIH, hydrocephalus, or an intracranial mass lesion produces elevated venous sinus pressure due to venous sinus collapse from external pressure. In that setting, elevated venous sinus pressure further impedes CSF egress. In IIH, standard time-of-flight magnetic resonance venography cannot distinguish between open sinuses with turbulent flow and complete or partial venous sinus occlusion. Time-of-flight methodology will eventually be replaced by auto-triggered elliptic centric-ordered sequence magnetic resonance venography, a bolus contrast delivery method of tracing venous blood flow which has recently shown that vessels with suspected partial occlusions were actually not occluded but had turbulence or “flow” artifact due to the time-of-flight technique (11,12).

King et al (13) have shown that in patients with IIH, there is a pressure gradient across a venous sinus stenosis that can be identified by intravenous transducers. They also found that this gradient could be eliminated by reducing
CSF pressure with removal of CSF through cervical puncture (13).

These observations are important because they cast doubt on the wisdom of placing venous sinus stents as treatment of elevated intracranial pressure due to IIH. The authors who promote this procedure have contended that by stenting collapsed or stenotic venous sinuses, not only is venous pressure relieved, but also CSF absorption into the sinuses is said to be enhanced across the pacchionian granulations (14). Because dural venous sinus stenting is a major, irreversible invasive procedure, more longitudinal follow-up data will be needed before it can be recommended widely.

There is much to think about in this trio of reports devoted to the problem of elevated CSF pressure. We must be scrupulous in applying names to conditions that have no explanation (IIH), especially when there are look-alikes that, if identified, would be managed differently. Perhaps it would be helpful to say “elevated intracranial hypertension caused by . . .” or “elevated intracranial pressure associated with . . .” In that way, intracranial pressure elevation in a person who also has cells in the CSF but no fever or other evidence of infection or tumor will not be written off as “pseudotumor cerebri with cells” or “pseudotumor syndrome with cells.” These terms deceive us into thinking we understand the pathophysiology.

The surgical review by Garton (2) provides an admirable assessment of the various surgical techniques available to treat increased CSF pressure. One might add subtemporal decompression as an additional option when CSF diversion or optic nerve sheath fenestration is inappropriate or ineffective.

When multiple treatment options are available for a condition, it could mean that no single treatment is overwhelmingly effective. This sentiment best summarizes the issues of causation and treatment of IIH. In addition to a randomized prospective trial of therapy currently in development, an animal model is needed. We have learned a lot about IIH, but we have a long way to go before it is clearly understood.

REFERENCES

Chronic Intracranial Hypertension with Unexplained Cerebrospinal Fluid Pleocytosis

Yaniv Barkana, MD, Neta Levin, MD, Yochanan Goldhammer, MD, and Israel Steiner, MD

Abstract: In a retrospective review of all cases with a diagnosis of idiopathic intracranial hypertension in two academic departments of neurology over a nine-year period, the authors identified six patients with a clinical course typical of idiopathic intracranial hypertension (IIH) except for the finding of cerebrospinal fluid pleocytosis. There were five women and one man with a mean age at presentation of 25.7 years (range, 25–32 yr). All were obese but had no other associated medical conditions or identifiable risk factors for IIH. In five patients, all or most cerebrospinal fluid cells were lymphocytes. Cerebrospinal fluid pleocytosis persisted for several months in all patients. Patients underwent a thorough laboratory and neuroimaging evaluation that did not reveal a primary cause. Medical treatment directed solely at lowering intracranial pressure was effective in five patients; one patient required lumboperitoneal shunting. Ophthalmic manifestations of increased intracranial pressure stabilized or remitted after treatment was withdrawn with a mean follow-up period of 33 months (range, 14–55 mo). Some patients may present with idiopathic chronic meningitis and elevated intracranial pressure that responds to treatment used for IIH.


METHODS

We reviewed the files of all patients who were hospitalized with the diagnosis of IIH from January 1991 to December 1999 in the departments of neurology of Sheba Medical Center, Tel Hashomer, Tel Aviv (Tel Aviv, Israel) and Hadasah-Hebrew University Hospital (Jerusalem, Israel). All patients who had CSF pleocytosis were identified and included in the present study. For these patients, data were collected from patient charts, including gender, age at presentation, obesity, symptoms and signs, CSF findings on presentation, results of diagnostic workup, and clinical course.

RESULTS

Over a nine-year period, six patients were identified with a clinical picture typical of IIH except for the presence of CSF pleocytosis. There were five women and one man. Mean age at presentation was 25.7 years (range, 17–32 yr). Mean follow-up was 33 months (range, 14–55 mo). Clinical data are summarized in Table 1.

All patients were obese, as defined by body mass index greater than 30 kg/m². Otherwise, none had associated
TABLE 1. Clinical course and outcome

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Obesity</th>
<th>Presenting symptoms</th>
<th>CSF cells/μL (% lymphocytes)</th>
<th>Protein (mg %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>Yes</td>
<td>TVOs</td>
<td>125 (100)</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>F</td>
<td>Yes</td>
<td>Headache, TVOs, nausea and vomiting</td>
<td>152 (90)</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>F</td>
<td>Yes</td>
<td>TVOs</td>
<td>66 (few)</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>F</td>
<td>Yes</td>
<td>Headache, TVOs, nausea and vomiting</td>
<td>38 (100)</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>F</td>
<td>Yes</td>
<td>Headache</td>
<td>16 (100)</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>F</td>
<td>Yes</td>
<td>Headache, vomiting, horizontal diplopia</td>
<td>65 (100)</td>
<td>43</td>
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</table>

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Opening CSF pressure (mm H₂O)</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
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<tr>
<td>50</td>
<td>&gt;400</td>
<td>Acetazolamide for 3 mo, then prednisone 60 mg/d for 3 mo, then open lumbar drain for 3 d, then LP shunt</td>
<td>Stabilized following LP shunt; irreversible inferior visual field defects in both eyes; bilateral optic disc pallor; visual acuity: 20/25 both eyes</td>
<td>55</td>
</tr>
<tr>
<td>56</td>
<td>&gt;400</td>
<td>Acetazolamide for 4 mo</td>
<td>Remained normal after therapy stopped</td>
<td>14</td>
</tr>
<tr>
<td>48</td>
<td>&gt;470</td>
<td>Acetazolamide for 12 mo</td>
<td>Remained normal after therapy stopped</td>
<td>29</td>
</tr>
<tr>
<td>52</td>
<td>500</td>
<td>Acetazolamide for 6 mo</td>
<td>Remained normal after therapy stopped</td>
<td>33</td>
</tr>
<tr>
<td>59</td>
<td>310</td>
<td>Acetazolamide for 5 mo</td>
<td>Remained normal after therapy stopped</td>
<td>31</td>
</tr>
<tr>
<td>55</td>
<td>380</td>
<td>Acetazolamide for 6 mo</td>
<td>Remained normal after therapy stopped</td>
<td>36</td>
</tr>
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</table>

CSF, cerebrospinal fluid; LP, lumboperitoneal; TVOs, transient visual obscurations.

Medical conditions or identifiable risk factors for IIH. All were afebrile throughout the clinical course. Upon presentation, all patients but one had bilateral swollen discs. All patients had elevated opening CSF pressures (range, 380–500 mm H₂O) and normal CSF glucose and protein values. The average number of white blood cells in the CSF on presentation was 77 cells/μL (range, 16–152 cells/μL). In #1, 4, 5, and 6, all cells were lymphocytes; in one patient (#2), 90% were lymphocytes; and in one patient (#3), the CSF contained predominantly polymorphonuclear leukocytes and a few lymphocytes. Five of the six patients had at least one additional CSF examination performed one to seven weeks after the initial spinal tap and performed as late as seven months after presentation (#1). Cerebrospinal fluid pleocytosis persisted in all repeated examinations, with a tendency to decrease in magnitude over time.

All patients underwent a thorough laboratory evaluation (Table 2). In none of the patients did it reveal a primary central nervous system or a systemic cause for the clinical picture.

Computed tomography scans of the brain and orbits were normal in all patients. Brain magnetic resonance imaging in four (#1, 3, 6, and 7) and magnetic resonance venography in one patient (#6) did not identify any cerebral or meningeal abnormalities (including enhancement).

Treatment with 250 mg acetazolamide every six hours resulted in prompt symptomatic relief in three patients (#2, 3, and 6) and gradual improvement over a period of several months in two (#4 and 5). These five patients remained asymptomatic following withdrawal of therapy.

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<tr>
<td>Cerebrospinal fluid</td>
<td>Serologic studies for EBV, HSV, CMV, VDRL, cryptococci: cultures for bacteria, chlamydia, viruses, and fungi; oligoclonal immunoglobulin G; ACE and ANA level; cytologic examination</td>
</tr>
<tr>
<td>EBV, Epstein-Barr virus; HSV, herpes simplex virus; CMV, cytomegalovirus, VDRL, Venereal Disease Research Laboratories; TPA-ABS, treponema pallidum antigen absorption; ACE, angiotensin-converting enzyme; ANA, antinuclear factor.</td>
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after four to 12 months. The one man (#1) did not respond adequately to medical treatment, requiring lumboperitoneal shunt.

**DISCUSSION**

In the present study, we report six patients who had chronic or subacute meningitis with intracranial hypertension and for whom the cause of CSF pleocytosis remained unexplained. Viewed alternatively, for these patients the criteria required for the diagnosis of IIH were met except for CSF pleocytosis because they presented with headache and papilledema without focal neurologic signs and neuroimaging did not disclose any intracranial abnormality. None of the patients had systemic symptoms or signs of an infectious or an inflammatory process. All underwent a comprehensive workup that did not disclose an infectious, inflammatory, or malignant cause during a mean follow-up period of 33 months.

Our patients had age and sex attributes typical for IIH. All had a course that resembles that of IIH, with five patients responding favorably to treatment with acetazolamide and one patient improving after lumboperitoneal shunt.

The pathogenesis of IIH is unknown. The syndrome may be due to an imbalance between the formation and the egress of CSF or a result of inability of intracranial structures, such as brain parenchyma and blood vessels, to accommodate increased volumes of CSF (1). Many conditions have been associated with the occurrence of the disorder, and in some, a cause-and-effect relationship has been established by clinical recovery following withdrawal of an exogenous causative agent and relapse upon repeat exposure (1).

Especially relevant are systemic conditions associated with the occurrence of IIH that are also capable of causing meningitis. Examples of such possible primary causes for IIH include several inflammatory, immune-mediated, or infectious disorders, such as systemic lupus erythematosus (4), Behçet disease (5), human immunodeficiency virus (HIV) infection (6), and Lyme disease (7). IIH has also been reported in epidemics following viral infection without meningitis (8). However, although all these diseases are recognized causes of meningitis, the cited case reports have not documented CSF pleocytosis.

CSF pleocytosis accompanies systemic infections with nervous system involvement in HIV infection (9), Lyme disease (10), and cryptococcal meningitis (11) and in association with sinusitis (12), but in none of these conditions has IIH been described. The pathogenetic mechanism linking the meningitis in the presented cases and the increased intracranial pressure is unclear. Both could be the independent outcome of a primary systemic condition. As an alternative, the meningitis could be the primary event and contribute to the occurrence of IIH by several mechanisms (such as impeding CSF absorption at the arachnoid villi). Considering that all patients were overweight, which is a known risk factor for IIH, it might be possible that obese patients are predisposed to develop IIH in some cases of meningeal inflammation. Whatever the mechanism, the presenting symptoms and the course of the disease in our patients are typical of IIH, and in all patients therapy for increased intracranial pressure and not for the meningitis led eventually to recovery.

Our series adds another syndrome to the list of conditions simulating IIH. Unquestionably, the presence of meningitis in such patients calls for an intensive evaluation to rule out an infectious, immune-mediated, or malignant underlying condition. However, when no cause for meningitis can be determined and the condition is chronic, we suggest that such idiopathic cases be treated as IIH. The term “pseudo pseudotumor cerebri” might be used to describe these patients. The association between meningitis and increased intracranial pressure may contribute to our understanding of the mechanisms responsible for IIH.

**REFERENCES**

Visual Hallucinations During Prolonged Blindfolding in Sighted Subjects

Lotfi B. Merabet, OD, PhD, Denise Maguire, BSc, Aisling Warde, BSc, Karin Alterscru, PhD, Robert Stickgold, PhD, and Alvaro Pascual-Leone, MD, PhD

Abstract: The authors report the occurrence of visual hallucinations of varying complexity in 13 normal subjects after sudden, complete, and prolonged visual deprivation. The subjects were all healthy individuals with no history of cognitive dysfunction, psychosis, or ocular pathology. They wore a specially designed blindfold for a period of five consecutive days (96 hours) and were asked to record their daily experiences using a hand-held microcassette recorder. Ten (77%) of the subjects reported visual hallucinations, which were both simple (bright spots of light) and complex (faces, landscapes, ornate objects). The onset of hallucinations was generally after the first day of blindfolding. Subjects were insightful as to their unreal nature. These results indicate that rapid and complete visual deprivation is sufficient to induce visual hallucinations in normal subjects.


Visual hallucinations arise under numerous conditions, such as psychiatric illness, sleep–wake transitional states, drug and medication use, and in various neurologic diseases (1,2). Furthermore, the deterioration of vision itself from pathology implicating the eyes or along the visual pathway can lead to visual hallucinations (1,2).

Visual hallucinations can be generally characterized as simple or complex, formed or unformed. Simple (or elementary) hallucinations often consist of spots of bright light generally referred to as phosphenes. In contrast, complex hallucinations consist of formed images such as faces, people, ornate objects, or landscapes (2,3). In conjunction with an ongoing study investigating the effects of visual deprivation on short-term brain plasticity, we observed the occurrence of visual hallucinations after rapid, complete, and prolonged blindfolding in normally sighted individuals.

METHODS

Subjects

The subjects of this report (n = 13) were all part of a group (n = 31) participating in a larger study. All experimental procedures were performed in accordance with the Declaration of Helsinki and were approved by the Beth-Israel Deaconess Medical Center Investigative Review Board and Harvard-Thorndike General Clinical Research Center. Subjects (five male and eight female) were between the ages of 18 and 35 (mean age, 25), medication-free, native English speakers without history of ocular, visual pathway, psychiatric, or neurologic disorder. All subjects had a normal neurologic and general physical examination performed by a physician.

Subjects were randomized to one of four groups, two of which were blindfolded (the 13 subjects reported here). Within this blindfolded cohort, one group was implicated in a tactile stimulation protocol (n = 7) while the other received no tactile stimulation (n = 6). Tactile stimulation included eight hours per day of activities stimulating the pads of their fingers. This involved four hours a day of intensive Braille instruction (supervised by a professional teacher from the Carroll School for the Blind, Newton, MA), two hours engaged in non-Braille tactile stimulation (tactile games, puzzles, clay modeling), and two hours spent in activities of daily living (ADL), including getting dressed, eating, walking around, and going to the gym. In accordance to our study protocol, all subjects were also involved in a serial functional magnetic resonance imaging (fMRI) to study brain activation in response to tactile stimulation of the index finger. The remaining study subjects were randomized to two non-blindfolded control groups, one with tactile stimulation (n = 9) and one without tactile stimulation (n = 9). The present report focuses on the experiences of the 13 subjects in the two blindfolded experimental groups.
Procedure

Subjects in the experimental groups were blindfolded for a period of 96 hours from 9 am on the first day until 4 pm on the fifth day. A specially designed blindfold was worn that prevented all light perception. It was held in place by a Velcro strap and further secured by Ace bandages. The blindfold permitted full motion of the eyes as well as opening and closing of eyelids. Potential tampering with the blindfold by the subjects was controlled with the use of a piece of photographic paper attached to the inside of the blindfold. All subjects were issued a hand-held microcassette recorder with automatic date/time stamping and directed to report their thoughts, feelings, and perceptions related to the experiment throughout the day as frequently as they desired. Each subject was also asked to report on the content of dreams every morning on awakening. The subjects were not prompted to describe their experiences and were unaware of the purpose of recording them.

RESULTS

Ten (77%) of the 13 blindfolded subjects reported visual hallucinations that varied in onset, duration, and content. Generally, the visual hallucinations began between the first day and second day of blindfolding and were of sudden onset, occurred while the patient was alert (regardless of whether the eyes were open or not), and vanished spontaneously. No subjects reported the ability to control volitionally the appearance or disappearance of the hallucinations. In a few cases, inciting factors were apparent, such as watching television or listening to music. Other sensory experiences, such as auditory or somatosensory sensations, were not reported.

In six of the 10 subjects who reported seeing hallucinations, the hallucinations were either simple (flashing lights or phosphenes) or complex (faces, hands, landscapes, ornate objects). In two of these six subjects, simple visual hallucinations evolved to more complex sensations as the blindfold period progressed. One subject reported seeing only simple visual hallucinations (“flashing lights”) and three subjects reported seeing only complex visual hallucinations. In some instances, the hallucinations were context appropriate, reflecting the subject’s psychologic state and changing in content and frequency as a function of the subject’s daily activities. For example, hallucinatory experiences were often reported when subjects were engaged in activities such as walking to and from testing sites or using the restroom. Interestingly, the hallucinatory experiences were never reported during periods of tactile stimulation such as Braille reading instruction or during fMRI sessions. According to the subjects’ own accounts, the hallucinations were always novel and had no relation to past experiences.

All subjects who experienced hallucinations did so during the blindfolded period. With one exception, the hallucinations ceased after the blindfold was removed on the fifth day. In one subject, they continued for a few hours after the blindfold was removed. Generally, subjects were initially disoriented after blindfold removal, reporting of transitory dizziness, and difficulty focusing. Vision returned to normal approximately 30 to 60 minutes after sight restoration. There were no apparent differences in the incidence or characteristics of the hallucinations between tactile-stimulated and non-stimulated blindfolded subjects. None of the subjects (n = 18) who were randomized to the control non-blindfolded groups experienced hallucinations. Here is a synopsis of the reported hallucinations:

Subject 1, a 29-year-old woman, experienced a single hallucination 12 hours after blindfolding. It occurred while she was standing in front of what she knew to be a mirror and was of a green face with big eyes. The subject became very frightened by the experience.

Subject 2, a 24-year-old man, experienced a broader range of images commencing a few hours after blindfolding and persisting for several hours after the blindfold was removed. Hallucinations at first included flashing lights, mirrors, lamps, trees, and full landscapes. At the conclusion of the second day of blindfolding, the images became more complex and he reported difficulty walking because of the “obstacles” he “saw.” For example, while taking a walk outside, he reported seeing “a ground of dirt rows, mounds of pebbles, or small stones that were running from upper left to lower right field of view and between them was running a small stream of water.” Over time, the images became a constant presence, and by the end of the study, he was reporting “ornate buildings of white-green marble” and “cartoon-like figures.”

Subject 3, a 24-year-old woman, reported one hallucinatory event. She had been napping while waiting for her sister to arrive for a visit. When her sister walked into the room, she opened her eyes and noticed a “splotch of light” in front of her eyes, “it was in the exact form of Elvis Presley...I pictured Elvis toward the center, maybe a little off to the left side...aligned with the nose a little bit more to the left and facing my left side...it was real distinct for some reason.”

Subject 4, a 23-year-old man, reported seeing images as well as flashes of light within a few hours of being blindfolded. He saw outlines of puzzle pieces that, while moving, “warped into other amorphous shapes” and transformed in color from white to orange to red. He saw these perceptions “when I think about my sense of sight.” On day four, he reported seeing a triangle with bold dots at each vertex of the triangle and “a large X with a light shining underneath...
Subject 5, a 29-year-old woman, reported seeing circles of light within 24 hours of blindfolding and again during the course of the week. On the second day, she reported, “I have the sensation that I can see my hands and my arms moving when I move them and leaving an illuminated trail.” She had this sensation as she reached to grab an object. When she realized that she could “see” her hands, she placed them in front of her face and observed their movement for several minutes. She also reported seeing images of bright half moons that moved in space.

Subject 6, a 34-year-old man, reported numerous instances of hallucinations that occurred when he would listen to the Mozart Requiem. In the first report, while listening to the music, he saw “the outline of a skull...it actually seemed to be turning and looking at me...sort of facing head-down and then face-down and then turning face-up...it seemed like it appeared in front of my eye.” On a second occasion, again while listening to the Requiem, he reported another instance of hallucinosis: “it was kind of a little scary and I also saw the outline of someone wearing some sort of ceremonial mask...it was fairly detailed. I could tell that there was some sort of headress...and the person seemed to have their face upturned and their mouth open. It was kind of brief—maybe two to three seconds or so.” On a third occasion, he reported, “I was listening to the Requiem again and I had an image of an older woman with a very wrinkled face. Her look was somewhat menacing, but what was interesting (she had white hair)...was that she was facing me. She seemed to be sitting in an airplane seat. But around her eyes she had a red eye shield similar to those one would wear...I really wish I could paint.” She also reported that the hallucinated objects were always “in motion,” stating “sometimes they would move fast and sometimes slower.”

Subject 8, a 20-year-old woman, experienced an array of hallucinations similar to those of #2. The hallucinations appeared suddenly 12 hours after blindfolding and evolved into a series of different images, much as in a dream. She reported seeing a butterfly that became a sunset, an otter, and finally a flower. She also reported seeing cities, skylights, kaleidoscopes, lions, and sunsets so bright she could “barely look at them.” “If there is a sunset or a sunrise I could not look at the sun...because it was too bright...it would seem like all of this light would just collect where the sun was and I just could not look there.” She stressed the intensity of the hallucinations, commenting “sometimes they were much prettier, I think, than anything I have ever seen...I really wish I could paint.” She also reported that the hallucinated objects were always “in motion,” stating “sometimes they would move fast and sometimes slower.”

Subject 9, a 27-year-old man, reported seeing flashes of light within 24 hours after blindfolding. Later in the week, he reported seeing images of resplendent peacock feathers and buildings.

Subject 10, a 21-year-old woman, reported a single intrusive hallucination a few hours after blindfolding. She reported this image as she was eating her first meal. As she sat facing her food tray, she reached over to another table and picked up a water pitcher so she could pour herself a glass of water. She reported that as the pitcher came into what would normally have been her field of view, “I felt like I was seeing the pitcher while I was pouring the water.”

**DISCUSSION**

Our study demonstrates that visual hallucinations of simple and complex types are common after sudden, complete, and prolonged visual deprivation in normal subjects. In agreement with previous reports, the hallucinations were vivid, well-defined, and consisted of simple and complex types (4–7). Subjects generally described their experiences as pleasant and amusing; in only two cases were the experiences fearful or intrusive to the point of interfering with the subjects’ ability to navigate within the environment.

Previous studies have reported results similar to ours. Subjects wearing opaque eye goggles put in darkened rooms experienced what authors termed “meaningful” hallucinations, including images of people, objects, and scenes (8,9). Linn et al (10) reported that after a three-day period of postoperative eye-patching, 18 of 21 patients aged between 45 and 85 showed “noticeable alterations in behavior,” including psychomotor disturbances, anxiety, and delusions.
Visual hallucinations, present in three of 21 patients, were often of other people. The hallucinations generally began within the second day of bandaging, progressed in severity on succeeding days, and disappeared once the bandages were removed. Ziskind et al (11) followed-up 98 patients aged between eight and 88 years old admitted for cataract surgery (88 patients patched for 24 hours) or retinal detachment (10 patients patched for seven to 14 days preoperatively and 14 to 30 days postoperatively). These patients were confined to bed and denied visitation for two days. Visual hallucinations occurred in all retinal detachment patients and in 30% of cataract patients. The greater prevalence of symptoms in the retinal detachment group was attributed to the longer period of patching. A potential drawback of these latter two studies is that patients were not controlled for use of medication or psychiatric disturbances.

The relatively high prevalence of hallucinations in our study may be explained by a number of reasons. First, our subjects were required to keep a microcassette recorder at hand at all times and instructed to report any unusual occurrences. Secondly, both eyes were suddenly and completely occluded for a prolonged period. Visual hallucinations have been reported to occur more frequently in acute, higher degrees of visual impairment and with bilateral monocular blindness (12-14).

The underlying neurophysiology of visual hallucinations remains a matter of debate. However, two general mechanisms have emerged. An “irritative” process may produce excitatory discharges originating within neighboring associative cortical areas (7,15). Alternatively, hallucinations may arise out of a “release” mechanism because of a lack of visual input to the brain. According to this hypothesis, visual deprivation interferes with normal inhibitory circuitry, resulting in inappropriate patterns of cortical excitation and abnormal central processing (2,7).

Blindfolding may represent a means to allow investigation of the effects of perturbing this normal inhibitory control. Activity within the visual cortex is presumed to be the product of incoming sensory signals, context-appropriate associations, and expectations that arise from multimodal cortices that feed back to unimodal cortices (16). Feedback connections from extrastriate cortical areas appear critical for visual awareness (17,18). When these dominating feedback inputs into the visual cortex are visual, visual hallucinations may occur. Other “phantom sensations,” such as auditory sensations in the recently deaf or phantom tactile sensations in amputees, may represent similar phenomena in different sensory domains (6).

Several of our subjects reported hallucinations that were context-appropriate. Examples are subject 1’s face in the mirror and 82’s pebbled pathways. Subject 3 “saw” Elvis when another person entered the room. Subject 5 “saw” her hands and arms when she reached to grab an object, and #10 “saw” the water pitcher when she reached over for it and it came into what would normally have been her field of view. These context-appropriate experiences may be the result of feedback projections arising from other associative cortical areas capable of “organizing” diffuse and random input and generating a structured percept.

The notion that visual hallucinations represent a condition in which a cessation of sensory inputs leads to an alteration in cortical processing has received experimental support. In the case of complete visual deprivation, Boroojerdi et al (19) have reported an increase in cortical excitability in the visual cortex as demonstrated with fMRI and transcranial magnetic stimulation. The effects were evident within minutes of visual deprivation. Howard et al (20) used fMRI during visual hallucinatory events and found that the occipital cortex manifests reduced responsiveness to exogenous stimulation, suggesting that this may underlie the disinhibition (or “release”) of endogenous visual memories whose content emerges into consciousness as hallucinations. Santhouse et al (7) have used fMRI and cross-correlated time series with hallucinatory events to identify associated cerebral activity during hallucinations. These authors argue that visual hallucinations are related to phasic increases in activity within visual cortical areas. Similarity between functional specializations of the activated cortical region and the content of the hallucination suggests that pathologic increases in activity within a specific component of the visual pathway lead to predictable visual hallucinatory content. For example, activation of the fusiform face area would correlate with perception of faces. Their findings also suggest that previous visual experience is an important contributor to the nature of visual hallucinations. This statement is supported by the fact that visual hallucinations have not been reported in the congenitally blind and only in the context of visual impairment (21).

The term “Charles Bonnet Syndrome” (CBS) has been used to describe patients with visual hallucinations with preserved intellectual function (4,22). Although the formal definition of the syndrome remains a matter of debate, most investigators agree that reduced or absent visual stimulation plays an integral part in the syndrome’s cause. The most common associated pathologies is age-related macular degeneration (2). The visual hallucinations described in this study fit with the current diagnostic criteria for CBS. First, the hallucinations were often vivid and complex, not associated with hallucinations in other sensory modalities, and subjects were insightful as to their unreality (23,24). Second, the hallucinations were the direct result of compromised visual input, a common cause for CBS (14,22,25).

Our subjects reported restful, undisturbed sleep and stated that being blindfolded had not affected their dreams.
Given that five of our subjects reported formed hallucinations on the day of blindfolding, one might predict that nocturnal hallucinations would be very common during subsequent sleep. Indeed, the hypnagogic hallucinations seen at sleep onset bear strong similarities to the images reported here (26, 27). The reported hallucinations bear some resemblance to objects that appear in dreams, particularly with regard to their unusual content. However, visual images reported during the study tended to be static and often context-appropriate, as opposed to the more complex and narrative visual hallucinations reported while dreaming (27). It has been proposed that visual hallucinations may lie along the continuum between the conscious reconstruction of previous perceptions and the spontaneous construction of dream-like sequences within the bounds of normal wakeful awareness (6). Whether the visual experiences reported in visual hallucinations and nocturnal dreaming share common neurophysiological mechanisms remains unclear. Our data do not shed light on this issue.

Acknowledgments

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REFERENCES

Bilateral Horizontal Gaze Palsy in Presumed Paraneoplastic Brainstem Encephalitis Associated With a Benign Ovarian Teratoma

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Abstract: A 28-year-old woman with a previous history of recurrent benign ovarian teratoma developed a bilateral horizontal gaze palsy, a right facial paresis, and bilateral trigeminal hypesthesia. Magnetic resonance imaging disclosed high signal in the rostral pons. Results of all other laboratory studies, including those for antineuronal antibodies (anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-Ma1, anti-Ma2, and anti-CV2/CRMP5), were negative. Pelvic ultrasound revealed a residual mass in the left ovary, which was confirmed as teratoma on surgical pathological examination. Complete neurologic recovery occurred within two weeks of surgical removal of the teratoma and treatment with intravenous corticosteroids and immunoglobulin. This case demonstrates that a search for an occult neoplasm is extremely important in the diagnosis of presumed paraneoplastic encephalitis even if antineuronal antibodies are not found.


Paraneoplastic syndromes are remote effects of cancer that are not directly related to tumor growth, metastases, metabolic or nutritional derangements, or side effects of therapy. The clinical manifestations of a paraneoplastic process are often the first presentation of an underlying tumor (1). Paraneoplastic encephalomyelitis–sensory neuropathy (PEM-SN) is a well-characterized syndrome that is typically irreversible and most commonly associated with small-cell lung cancer and anti-Hu antibodies (2). The clinical manifestations are variable, including multifocal involvement of the central or peripheral nervous system or both, and brainstem or limbic encephalitis. There are a few case reports of supranuclear, nuclear, or internuclear oculomotor abnormalities affecting horizontal or vertical eye movements or both in patients with PEM-SN (3-8). We report a case of complete bilateral horizontal gaze palsy in a patient with a presumed paraneoplastic brainstem encephalitis associated with a benign ovarian teratoma. Surgical removal of the tumor, combined with intravenous corticosteroid and immunoglobulin treatment, rapidly reversed all neuro-ophthalmic manifestations.

CASE REPORT

In 1998, a 28-year-old woman of Chinese descent developed impaired memory, personality change, auditory hallucinations, inappropriate behavior, and hypersomnia followed by acute central respiratory failure that required mechanical ventilation. Findings on magnetic resonance imaging (MRI) scans and extensive laboratory workups were normal, except for a mild cerebrospinal fluid (CSF) pleocytosis and minimal electroencephalographic bilateral background irregularities. A palpable pelvic mass was confirmed on ultrasound and computed tomography as a 14 × 10 × 10-cm complex cystic lesion in the right ovary. Neurologic symptoms resolved eight weeks after a complete right salpingo-oophorectomy and removal of a mature cystic ovarian teratoma, in conjunction with 400 mg/kg intravenous immunoglobulin (IVIG) per day for five days and 1 g intravenous methylprednisolone daily for five days, followed by a gradual taper of oral prednisone starting at a daily dose of 60 mg.

Nearly three years later, she developed slurred speech. An MRI scan showed a small, hyperintense T2-
weighted signal in the dorsal posterior aspect of the medulla just anterior to the fourth ventricle. Again, findings on extensive laboratory testing, including CSF oligoclonal bands and evoked potentials, were normal. Ultrasonography revealed the presence of two small, 2-cm cystic masses in the left ovary that were not present at the time of her first illness. Six weeks after partial left salpingo-oophorectomy with resection of a benign ovarian teratoma and IVIG and corticosteroid therapy, her neurologic manifestations resolved (9).

Seven months later, she developed a one-week history of progressive diplopia, numbness of both sides of the face (including the anterior half of the tongue), and ataxia. Visual acuity was 20/20 in each eye. Pupils, visual field, color vision, and findings on slit-lamp and funduscope examinations were normal. She had a complete bilateral horizontal gaze palsy affecting saccades, smooth pursuit, and the vestibulo-ocular reflex (VOR). Vertical eye movements and convergence were normal. She had reduced sensation to pinprick over the face and anterior scalp bilaterally. A mild right facial weakness was present. Corneal sensation was mildly reduced OD. She had moderate difficulty with tandem gait. Mental status examination was normal. Results of cardiovascular, respiratory, and abdominal examinations were normal.

Findings on investigation of the following were all normal: complete blood cell count; electrolytes, creatinine, blood urea nitrogen, glucose, calcium, magnesium, and phosphate; INR, partial thromboplastin time, AST, ALP, bilirubin, lactate dehydrogenase, creatine kinase, and C-reactive protein; CSF studies (cell count, oligoclonal bands, glucose, protein, albumin, Venereal Disease Research Laboratories test, immunoglobulin G [IgG], polymerase chain reaction for cytomegalovirus, herpes simplex virus, and Epstein-Barr virus, immunofluorescent assay for cytomegalovirus, cryptococcal antigen, bacterial, viral and fungal cultures); anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, ANCA, rheumatoid factor, anti-centromere, antimitochondrial, and smooth muscle antibodies; cryoglobulin, C3, C4, human immunodeficiency virus (HIV), hepatitis B and C serological testing; alpha feto-protein and Ca125 tumor markers; antineuronal antibodies (anti-Hu,
anti-Yo, anti-Ri, anti-Tr, anti-Ma1, anti-Ma2, and anti-CV2/CRMP5; visual, somatosensory, and brainstem auditory evoked potentials; chest x-ray; urinalysis; and beta-HCG. Serum immunoglobulin quantification revealed an elevated IgG level (31.9 g/L) and normal immunoglobulin A and immunoglobulin M levels, with no M-spike.

Pelvic ultrasound revealed a 1.7 x 1.5 x 1.1-cm mass in the left ovary, consistent with a residual or recurrent teratoma. Brain MRI scan demonstrated a region of hyperintense signal on T2-weighted scan and FLAIR in the midline dorsal pons involving the facial colliculus extending to the floor of the fourth ventricle (Fig. 1). No abnormality was found in the cerebral hemispheres.

The patient was started on a daily regimen of 1 g intravenous methylprednisolone and 24 g IVIG. Despite treatment, she continued to deteriorate with new onset of dysphagia after five days. She underwent a partial left salpingo-oophorectomy. Surgical pathological findings revealed a benign residual cystic teratoma characterized by a small, keratin-filled cyst of 1.4 cm in maximum dimension with an associated granulomatous reaction (Fig. 2). Following surgery, she was treated with another three-day course of 24 g IVIG daily. Within two weeks after surgery, her bilateral horizontal gaze palsy, dysphagia, and bilateral facial numbness had resolved. She was discharged on a tapering dose of oral prednisone and remained free of symptom at a 10-month follow-up.

**DISCUSSION**

Our patient, who had history of recurrent benign ovarian teratoma, manifested recurrent central nervous system (CNS) symptoms and signs, starting with a limbic encephalopathy and later brainstem involvement. All neurologic manifestations disappeared promptly after surgical removal of the teratoma, in combination with corticosteroid and IVIG therapy.

In the most recent episode, she presented with a brainstem encephalitis manifested by hypesthesia in the trigeminal distribution, bilateral horizontal gaze palsy, and a right lower motor neuron facial paresis. The absence of horizontal saccades, smooth pursuit, and VOR, with sparing of convergence, was consistent with a lesion in the sixth nerve nuclei bilaterally, with or without involvement of the paramedian pontine reticular formation.

It is conceivable that the tumor was a coincidental finding and that the neurologic manifestations were due to another disease process. However, results of our extensive investigations for an infectious, vascular, or other neoplastic condition were negative. A relapsing demyelinating disease is unlikely, considering the prolonged psychiatric disturbance followed by acute central respiratory arrest, normal laboratory findings (including the absence of oligoclonal bands in the CSF), the absence of white matter abnormalities in either hemisphere on multiple MRI scans, and the dramatic recovery following surgical resection of the tumor in each episode. These phenomena support a diagnosis of paraneoplastic encephalitis.

PEM-SN, first described by Henson (10) in 1965, is a rare disorder with variable clinical manifestations depending on the location of degeneration in the central or peripheral nervous system, or both. Dalmau et al (11) found that 78% of patients with PEM-SN and anti-Hu antibodies in their serum had small-cell lung cancer, whereas 13% had no detectable tumor. Other malignancies associated with PEM-SN include ovarian and breast carcinomas, Hodgkin's disease, non-Hodgkin's lymphoma, other lung tumors, and cancers of the gastrointestinal tract, kidney, bladder, and prostate gland (1). Seventy-three percent of patients with PEM-SN present with multifocal involvement of the nervous system (11). Predominant findings include...
sensory neuronopathy (62%), motor neuron dysfunction (20%), limbic encephalopathy (20%), cerebellar involvement (15%), brainstem encephalopathy (14%), and autonomic nervous system dysfunction (10%) (11).

A number of antibodies have been associated with PEM-SN (2,12). Because the sensitivity of available tests for these antibodies is only 50% to 60% (12), the diagnosis of PEM-SN should be entertained even without positive serological findings.

Pathologically, PEM-SN is characterized by glialosis and glial nodule formation, neuronal loss and degeneration, and perivascular lymphocytic infiltration without concomitant vasculitis in small arterioles (13). Treatment consists of removal of the underlying tumor. Immunomodulatory therapy using corticosteroids, plasmapheresis, or IVIG is rarely effective (11,14), but improvement has been reported in single patients (15,16). Even with tumor removal, the majority of patients have progressive neurologic decline, often ending in death within weeks to months as a result of autonomic dysfunction or respiratory failure of central or neuromuscular origin (11). There are a few cases with an indolent (17) or fluctuating (18,19) natural course, as well as those with spontaneous improvement of neurologic symptoms (20) or tumor regression (21).

Our patient is the first documented case of complete bilateral horizontal gaze palsy secondary to a reversible presumed paraneoplastic brainstem encephalitis associated with a benign ovarian teratoma. There have been two other reported cases of limbic encephalitis associated with immature ovarian teratomas. In both cases, antineuronal antibodies were not detected and symptoms improved or stabilized after tumor removal (22,23). In fact, our patient's initial presentation was in many ways similar to these two reported cases, lending further support to a paraneoplastic origin.

Ocular motor abnormalities have been associated with several different CNS paraneoplastic syndromes. In subacute paraneoplastic cerebellar degeneration, there have been descriptions of downbeat, upbeat, rotary, gaze-evoked, and rebound nystagmus, as well as opsonic, ocular flutter, saccadic dysmetria, saccadic pursuit, and skew deviation (1). In paraneoplastic opsonolus syndrome, involuntary, arhythmic, multidirectional saccades in all three dimensions have been documented (24).

Supranuclear, nuclear, and internuclear abnormalities of ocular motility have been described in PEM-SN, but not with a benign ovarian teratoma (3–8). Baloh et al (4) reported two patients with prostate cancer who had selective loss of horizontal saccades with sparing of horizontal slow eye movements. Postmortem examination revealed perivascular chronic inflammatory cells and microglial infiltration of the pons and medulla; neuronal loss in the pontine tegmentum, medulla, and cerebellum, but preservation of brainstem motor nuclei. Both patients had prominent inflammatory cell infiltrates and microglial nodules in the paramedian pontine reticular formation, accounting for the selective loss of horizontal saccades. Neither patient had antineuronal antibodies detected in the blood.

Crimo et al (13) reported three patients with ophthalmoplegia who had paraneoplastic brainstem encephalitis. One of them, who had a small-cell lung cancer and anti-Hu antibodies, had a bilateral horizontal gaze palsy affecting saccades, pursuit, and the VOR. Another patient had a complete external ophthalmoplegia and positive anti-Hu antibodies, but no evidence of systemic malignancy. On postmortem examination, the oculomotor, abducens, and trochlear nerves were devoid of normal neurons. A third patient exhibited supranuclear ophthalmoplegia with profoundly reduced voluntary vertical and horizontal eye movements. Anti-Hu antibodies were negative. Following a course of methylprednisolone, the patient's neurologic status continued to decline, and she subsequently died of pneumonia. On postmortem examination, a papillary follicular thyroid carcinoma and an uterine leiomyoma were detected.

Pillay et al (5) described internuclear ophthalmoplegia and “optic neuritis” in a patient with bronchial carcinoma. Pathological examination revealed secondary demyelination of the medial longitudinal fasciculus and focal neuronal loss in the nuclei of the third, fourth, and sixth nerves. Ruchy and Vakili (6) described a patient with midbrain encephalitis and lung cancer who had a bilateral third nerve palsy. Pathological correlation revealed focal neuronal loss and glialosis involving the oculomotor nuclear complex.

Schiff et al (7) reported a patient with small-cell carcinoma of the lung and anti-Hu-associated encephalopathy, with vertical gaze paresis, absent downgaze, poor fixation, and hypometric horizontal saccades. Bennett et al (8) reported two patients with testicular cancer who exhibited supranuclear gaze disorders as a manifestation of PEM-SN. The first patient had a vertical gaze palsy with oculogyric crisis, lid retraction, and ocular tilt reaction. The second patient had a left hypertropic skew deviation, accompanied by a fluctuating, mixed pendular and jerk nystagmus. Both were positive for anti-Ta antibodies.

In our case, we presume that an immune response directed against the teratoma cross-reacted with normal brain antigens and caused the varied neurologic symptoms each time the tumor recurred. Specific antineuronal antibodies were not identified in our case or in the two reported cases of PEM-SN associated with immature ovarian teratoma (22,23). Whether such antibodies exist or, as an alternative, whether teratoma-associated paraneoplastic disorders arise from a cell-mediated mechanism is not known.
The present case demonstrates that a search for an occult neoplasm is extremely important in the presence of an unexplained encephalitis even if conventional paraneoplastic antibodies are absent. Resection of the tumor, even a benign one, may lead to symptom resolution. Although immunomodulatory therapy is not uniformly effective, empiric treatment with these agents may also be beneficial.

REFERENCES

Metastatic Neuroblastoma Presenting with Binocular Blindness from Intracranial Compression of the Optic Nerves

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Abstract: A 2-year-old boy with blindness as an isolated symptom was found to have no light perception binocularly because of compression of both optic nerves by a neuroblastoma infiltrating the walls of the optic canals and medial sphenoid bone. Imaging disclosed a primary tumor near the kidney and multiple osseous metastases. Although neuroblastoma commonly causes blindness by metastasis to the orbit, it rarely causes bilateral blindness from intracranial compression of the optic nerves. This is the first report of bilateral blindness as the presenting feature.

Several reports (1-13) have documented ophthalmic complications of metastatic neuroblastoma. When visual loss occurs, it is nearly always from optic nerve compression by an orbital metastasis causing proptosis (often ecchymotic) and ductional restriction. We describe a two-year-old boy who presented with binocular blindness from a planum sphenoidale region metastatic neuroblastoma. It compressed both optic nerves as they emerged from the intracranial portion of the optic canals. There was no clinical or imaging evidence of orbital invasion. Among the reported cases, only one (12) is similar to ours. In that case, a 2-year-old boy with antecedent malaise, irritability, and anorexia eventually developed bilateral blindness from a sphenoidal region neuroblastoma compressing both optic nerves. In that case, no primary tumor was found.

CASE REPORT

A two-year-old boy reported that he suddenly could not see. His parents had noted that for several days he had been stumbling into objects. During the previous month, he had paid several visits to a pediatrician for fever that led to a diagnosis of otitis media. He was the product of a normal pregnancy and delivery and had no other health problems.

Ophthalmic examination verified no light perception in either eye. The globes and their adnexa were normal. There was no proptosis or resistance to repositioning. The eyes were aligned and moved normally. Pupils measured 7 mm in dim illumination and did not constrict to light. Biomicroscopy and ophthalmoscopy were normal. The rest of his physical examination was unremarkable.

Brain magnetic resonance imaging (MRI) scans (Figs. 1A, 2A and B, and 3A) showed a heterogeneous mass centered at the level of the planum sphenoidale, permeating bone, encasing the intracranial optic nerves, and involving the paranasal sinuses and nasopharynx. Signal characteristics suggested neoplasm or unusual infection. The patient was placed on intravenous dexamethasone. Transnasal biopsy of a left ethmoid mass showed a densely cellular neoplasm composed of small cells with oval to irregular nuclei, granular chromatin, and scant cytoplasm (Fig. 4A). One day after the biopsy, the patient still had no vision, so he underwent a transcranial decompression, mainly of the right side of the tumor. A postoperative brain MRI showed moderate decompression of the right optic nerve, less so of the left optic nerve (Figs. 1B, 2C, and 3B). Pathologic specimens again showed a small cell neoplasm forming well-defined nests with abundant associated neuropil, separated by fibrovascular septa, morphologically consistent with a poorly differentiated, Schwannian stromal-poor neuroblastoma with a low mitotic-karyorrhectic index (Fig. 4B). Immunohistochemical studies showed that the tumor cells were strongly positive for protein gene product 9.5 (PGP9.5) and negative for MIC-2, supporting a diagnosis of neuroblastoma (Fig. 4C). Bone marrow aspiration revealed the presence of metastatic neuroblastoma cells (Fig. 4D).

Computed tomography (CT) scans of the chest, abdomen, and pelvis were normal except for a 3 x 2-cm mass
FIG. 1. A: Preoperative coronal enhanced T1-weighted MRI shows an intensely enhancing soft tissue mass at the ethmoid sinus that permeates the bone and is contiguous intracranially along the planum sphenoidale and posterior orbital roof and elevates the brain. B: Postoperative coronal enhanced T1-weighted MRI shows a residual soft tissue mass in the ethmoid region, and at left planum sphenoidale.

anterior to the middle pole of the left kidney (Fig. 5A). A 123I-metaiodobenzylguanidine (MIBG) scan showed abnormal uptake in the left perirenal area and at multiple bony sites, including the spine, pelvis, femur, and humerus. Based on the presence of widespread metastatic disease, a diagnosis of stage 4 neuroblastoma was made, and treatment was initiated on the current Children’s Oncology Group protocol for high-risk neuroblastoma.

Four weeks after the decompression and initiation of chemotherapy, the patient could accurately reach for coins. Both optic discs were slightly pale. An afferent pupil defect was present OS.

After five cycles of chemotherapy, the patient underwent laparoscopic resection of the left pararenal mass, most likely arising from a portion of the adrenal gland. Histologic examination revealed a treated neuroblastoma showing a spectrum of apparent differentiation (Fig. 5B).

In addition to chemotherapy and surgery, he has undergone an autologous bone marrow transplant, as well as treatment with both 13-cis retinoic acid and 3F8 (anti-GD2) antibody. Now 18 months from the time of initial diagnosis, the patient remains in clinical remission. Visual acuity is 20/400 OD, hand movements OS, with an afferent pupil defect OS and markedly pale optic discs. No additional neuro-ophthalmic deficits have appeared.

DISCUSSION

The initial clinical manifestation of our young patient with metastatic neuroblastoma was binocular blindness. Visual loss occurs in metastatic neuroblastoma, but it is virtually always based on orbital invasion and is usually monocular. Our case simply represents a more posterior and midline sinocranial deposit that affected the intracranial optic nerves bilaterally.

In reporting the ophthalmic manifestations of metastatic neuroblastoma, Musarella et al (8) found orbital metastases in 60 (75%) of 80 children. There are four previous reports of neuroblastoma presenting with visual loss but without orbital manifestations (4,11-13). In a retrospective review of 450 neuroblastoma patients, Belgaum et al (4) reported one patient with sudden onset of monocular visual loss without orbital manifestations but no further details are given. In the fourth and fifth editions of Walsh & Hoyt’s Clinical Neuro-Ophthalmology, Miller (11) described a 22-year-old man who developed progressive monocular optic neuropathy from a neuroblastoma deposited on the sphenoid bone. Varma et al (12) described a two-year-old boy with bilateral blindness because of compression of both optic nerves from a neuroblastoma situated in the sphenethmoidal region. Their case differs from ours in that the child had premonitory constitutional symptoms of malaise, irritability, and anorexia. In our patient, the visual loss was the only reported or observed manifestation. Shubert et al
FIG. 2. A: Preoperative axial T2-weighted MRI shows a low T2-signal mass along the planum sphenoidale and a low signal band of dura separating it from brain parenchyma. B: Preoperative axial enhanced T1-weighted MRI shows intense enhancement of the extradural mass. C: Postoperative axial enhanced T1-weighted MRI shows small enhancing residual mass on the left planum.

(13) reported a two-year-old girl with bilateral blindness and disc edema who also had total left ophthalmoplegia and left upper lid ecchymosis. Autopsy revealed metastatic neuroblastoma in the anterior and middle fossae compressing both optic nerves and extending through the superior orbital fissure into both orbits. Transverse sinus thrombosis had probably caused elevated intracranial pressure. The primary tumor was suprarenal.

Neuroblastoma, the most common extracranial solid tumor of childhood (8% of pediatric cancers), arises from cells of the neural crest of any site within the sympathetic nervous system, but an abdominal locus is most common (13). Most patients (>90%) are diagnosed before age 10, the most frequent clinical presentation being that of an abdominal mass. Yet up to 50% of patients have metastatic disease at the time of diagnosis. Paraneoplastic manifestations such as opsoclonus-myoclonus or cerebellar ataxia are seen in 4% of patients. Imaging studies important for staging include CT and MRI, as well as MIBG scanning. Preferentially taken up by adrenergic secretory vesicles present...
FIG. 4. A: Transnasal biopsy of left ethmoid sinus shows a densely cellular neoplasm composed of small cells and associated neuropil, forming sheets and vague nests. The tumor cells occupy the entire respiratory mucosa in this fragment, but respect the epithelium and glandular structures (hematoxylin and eosin, ×200). B: Skull base tumor from craniotomy shows well-defined nests of tumor cells with abundant associated neuropil, separated by fibrovascular septa (hematoxylin and eosin, ×200). C: Immunohistochemical studies show that the tumor cells have strong cytoplasmic reactivity for PGP9.5 (left, magnification ×200) but are negative for CD99 (MIC-2) (right, magnification ×200). D: Bone marrow biopsy shows interstitial, sinusoidal, and sheet-like infiltrates of tumor cells occupying much of the intertrabecular space (hematoxylin and eosin, ×200).

in neuroblastoma (and adrenal medullary) cells, MIBG has proven to be a sensitive technique to identify sites of metastatic disease and to evaluate response to treatment (14).

The initial transnasal biopsies in this case showed a small round cell neoplasm, the differential diagnosis of which included, in addition to neuroblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET), and esthesioneuroblastoma. Non-Hodgkin lymphoma and rhabdomyosarcoma involving the orbit or paranasal sinuses can present clinically in children as acute bilateral blindness (15–17). Ewing sarcoma/PNET has been reported as a primary neoplasm of skull bones and sinuses (17–22) and also as a metastatic lesion (23). A primary Ewing sarcoma/PNET of the orbit has been associated with unilateral visual loss (24). Esthesioneuroblastoma is a much less common tumor, especially in young children, and typically presents with a different set of symptoms (25), but presentation with sudden visual loss has been described (26–28).

The subsequent specimens obtained at craniotomy showed tumor cells forming nests with neuropil, providing evidence of neuroectodermal differentiation, which argued against non-Hodgkin lymphoma and rhabdomyosarcoma. The morphologic differential diagnosis could reasonably then be narrowed to neuroblastoma, Ewing sarcoma/PNET, and esthesioneuroblastoma.

Neuroblastoma and Ewing sarcoma/PNET can show similar morphology. Immunohistochemical studies of PGP9.5 (29) and MIC-2 expression are very helpful in dist-
Metastatic Neuroblastoma with Binocular Blindness

FIG. 5. A: Axial enhanced abdominal CT scan of abdomen shows a left para-aortic pararenal soft tissue mass (arrows) that is possibly the primary site of neuroblastoma. B: Resection of left pararenal mass after five cycles of chemotherapy shows neuroblastoma with treatment effect, resulting in appearances ranging from those of differentiating neuroblastoma (shown here) to maturing ganglioneuroma (hematoxylin and eosin, ×200).

Distinguishing between these tumors. Neuroblastoma is typically positive for PGP9.5 and negative for MIC-2 expression, whereas Ewing sarcoma/PNET is generally positive for both markers (30–32). In this case, the immunophenotypic profile was that of neuroblastoma.

Esthesioneuroblastoma cannot necessarily be excluded morphologically or immunophenotypically. These tumors can show a range of appearances from lesions closely resembling neuroblastoma to lesions resembling neuroendocrine carcinoma (33). Distinction from neuroblastoma can generally be made on clinical grounds. In addition, neuroblastomas differ genetically from esthesioneuroblastomas (33). However, if a primary neuroblastoma is not identified elsewhere, and genetic studies are not available, it could be difficult to decide if a sinus mass is best considered a neuroblastoma or an esthesioneuroblastoma. In this case, the subsequent demonstration of an abdominal primary tumor excluded esthesioneuroblastoma.

Patients with localized disease (stages 1, 2) have a better prognosis than those with neuroblastoma that has metastasized to distant sites (stage 4), including bone and bone marrow (34). Other features associated with a poor prognosis are unfavorable histology, amplification of the MYCN oncogene, characteristic chromosomal losses (1p) and gains (17q), age older than one year, and elevated ferritin and urinary catecholamine levels (35).

Treatment of neuroblastoma involves chemotherapy, surgery, radiation, and autologous bone marrow transplantation, which is used as a rescue following marrow-ablative induction chemotherapy.

Patients with localized disease have a 95% cure rate; those with intermediate stage neuroblastoma have a 70% to 80% cure rate; those with advanced disease have only a 20% to 30% cure rate. Recent therapeutic advances include the use of differentiating agents such as 13-cis-retinoic acid in an attempt to improve outcome (34). It is thought that retinoic acid causes decreased proliferation, decreased expression of the MYCN oncogene, and morphologic differentiation to mature, nondividing cells. In addition, immunotherapy using the murine 3F8 antibody (directed against the GD2 surface antigen present on neuroblastoma cells) is undergoing experimental evaluation (35,36). Preliminary studies indicate feasibility and efficacy of this novel treatment modality. Finally, ¹³¹I-MIBG has been used to selectively target radiation to residual or recurrent neuroblastoma in association with myeloablative chemotherapy and hematopoietic stem cell rescue (37). Although promising, the impact of these novel therapies on the long-term survival of patients with stage 4 neuroblastoma remains to be determined.

REFERENCES

Visual Manifestations of Visible and Buried Optic Disc Drusen

Jay M. Wilkins, MD and Howard D. Pomeranz, MD, PhD

Background: It has been reported that visible optic disc drusen are associated with decreased visual acuity and loss of peripheral visual field. Patients with buried optic disc drusen have not been as well characterized.

Methods: An observational, retrospective review was made of 92 eyes with funduscopic or ultrasonographic evidence of optic disc drusen. Demographics, presenting symptoms, visual acuity, refractive error, intraocular pressure, presence of an afferent pupillary defect, cup-to-disc ratio, appearance of the optic nerve, and visual field were recorded.

Results: Fifty-one (55%) of the eyes were symptomatic; among them, 63% had symptoms of visual acuity loss, and 49% had symptoms of visual field loss. Seventy-nine (86%) of the optic discs appeared abnormal on ophthalmoscopy, but only 42% of these had visible drusen. Forty-five (49%) of the eyes had a visual field defect, and 73% of these were nerve fiber bundle in type. Overall, 73% of optic discs with visible drusen had abnormal visual fields compared with only 36% of optic discs with buried drusen ($P < 0.05$).

Conclusions: Among 92 eyes with optic disc drusen, only slightly more than 50% produced visual symptoms. Fewer than 50% of drusen were visible ophthalmoscopically. Buried optic disc drusen identified by ultrasound had a significantly lower frequency of associated visual field defects than did visible optic disc drusen.

(Optic disc drusen are hyaline, often calcified, bodies located in the prelaminar portion of the optic nerve head. These abnormalities are thought to be due to degeneration of axons. There are two types of drusen: (1) visible drusen, which protrude from the disc and are particularly prominent at the disc margin and the nasal portion of the optic disc, and (2) buried drusen, which are not directly visible but can cause elevation of the optic disc with blurred or obscured optic disc margins. Anomalous retinal vessels that have increased branching, looping, or tortuosity often accompany this elevation.)
The objective of the present study was to characterize the visual manifestations related to visible and buried drusen. Only optic discs with visible drusen or definitive ultrasonographic evidence of buried drusen were included.

**METHODS**

Institutional Review Board/Ethics Committee approval (0209E33201) was obtained. We retrospectively reviewed all records from the University of Minnesota eye clinic (Minneapolis, MN) with the diagnosis of optic disc drusen (ICD-9 code 377.21) between July 1, 2001 and December 31, 2002. We collected the following data: demographics, presenting symptoms, visual acuity, refractive error, intraocular pressure, presence of an afferent pupillary defect, cup-to-disc ratio, appearance of the optic nerve, and visual field (Humphrey or Goldmann). Patients were excluded if they were inappropriately coded, had incomplete records, or lacked definitive funduscopic or ultrasonographic evidence of optic disc drusen. Patients were also excluded if they had a coexisting ocular diagnosis that potentially affected the optic nerve, visual acuity, or visual field, such as glaucoma or ischemic optic neuropathy. With these exclusions, none of the patients in the present study had any conditions that could cause abnormalities of visual acuity or visual field other than optic disc drusen. None of the patients in the present study had tuberculosis sclerosis, retinitis pigmentosa, pseudoxanthoma elasticum, or angioid streaks.

Presenting symptoms were categorized as asymptomatic or symptomatic (visual acuity loss or visual field loss). Appearance of the optic nerve was categorized as normal, visible drusen, or elevated disc/anomalous vasculature. Visual fields were categorized as follows: normal, nerve fiber bundle defect, generalized constriction, or increased blind spot. When available, Humphrey visual fields were used instead of Goldmann visual fields because they were deemed more accurate and easier to categorize. If more than one presenting symptom or visual field defect was present, each was tabulated separately. The author (HDP) classifying the visual field was masked to the appearance of the optic disc. A nerve fiber bundle defect was defined as one that originated from the blind spot and extended in a curvilinear fashion without crossing the horizontal midline. A generalized defect was defined as one that produced diffuse or peripheral loss without respecting the vertical or horizontal midline. An enlarged blind spot was defined as a defect that expanded the borders of the normal physiologic blind spot without extending into a curvilinear arcuate defect.

B-scan ultrasonography was performed using a "non-contact" method, with placement of the probe on the closed eyelid (over methylcellulose), not in direct contact with the globe. The optic nerve was centered in a vertical axial view for examination of optic disc drusen. Buried drusen were diagnosed if a highly reflective echographic signal persisted as the gain was decreased from 75 to <27 dB (10-MHz probe, P system, ABD, Innovative Imaging Inc., Sacramento, CA). Normal-appearing optic nerves were scanned only if the optic nerves appeared abnormal in the fellow eye.

Statistical analysis was performed to determine whether a relationship existed between optic disc appearance and Humphrey visual field parameters. P values were calculated by t test on two populations (buried drusen and visible drusen) using Origin 6.1 computer software. Numerical data are shown as mean ± standard error (SE).

**RESULTS**

Complete records of 124 eyes from 70 correctly coded patients were reviewed. During the study time period, 14,427 patients were seen in the University of Minnesota eye clinic. This resulted in a prevalence of optic disc drusen of 0.49% in our clinic population. Fifteen of the eyes were excluded because they lacked definitive funduscopic or ultrasonographic evidence of optic disc drusen. Seventeen additional eyes were excluded because of a coexisting ocular diagnosis that could potentially affect the optic nerve, visual acuity, or visual field analysis. This included one amblyopic eye that was excluded because it was not successfully treated to within two lines of the visual acuity of the fellow eye. Forty-six of 63 patients (73%) had evidence of bilateral optic disc drusen before some eyes were excluded because of coexisting diagnoses.

The remaining 92 eyes from 56 patients were the subjects of the present study. Patient age ranged from eight to 69 years (mean, 38.9 years). There were 38 (68%) female and 18 (32%) male patients. Forty-eight of the eyes were designated OD, and 44 OS. Presenting symptoms are listed in Table 1. Seven eyes had more than one presenting symptom. Fifty-one (55%) eyes were symptomatic, presenting with a complaint of visual acuity loss or visual field loss.

Visual acuity ranged from 20/15 to 20/50 with a mean logarithmic Minimum Angle of Resolution visual acuity of 0.01 ± 0.01 (20/20). Eight eyes had a visual acuity worse than 20/25 (Table 2). Sixty-five eyes had a recorded refractive error, including 47 (72%) myopic eyes and 16 (25%)

<table>
<thead>
<tr>
<th>TABLE 1. Presenting visual symptoms in patients with optic disc drusen</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Symptomatic</td>
</tr>
<tr>
<td>Visual acuity loss</td>
</tr>
<tr>
<td>Visual field loss</td>
</tr>
</tbody>
</table>
Visible and Buried Optic Disc Drusen

TABLE 2. Visual Acuity in Patients with Optic Disc Drusen

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Number (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/15</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>20/20</td>
<td>59 (64%)</td>
</tr>
<tr>
<td>20/25</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>20/30</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>20/40</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>20/50</td>
<td>1 (1%)</td>
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</table>

TABLE 4. Prevalence of Visual Field Defects in Patients with Optic Disc Drusen

<table>
<thead>
<tr>
<th>Visual Field Defect</th>
<th>Number (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No defect present</td>
<td>47 (51%)</td>
</tr>
<tr>
<td>Defect present</td>
<td>45 (49%)</td>
</tr>
<tr>
<td>Nerve fiber bundle</td>
<td>33 (73%)</td>
</tr>
<tr>
<td>Generalized constriction</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Increased blind spot</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

hyperopic eyes; the mean spherical equivalent was \(-2.43 \pm 0.45\) D. The mean intraocular pressure by applanation or Tonopen examination was \(15.5 \pm 0.3\) mm Hg.

Only three (3%) eyes had an afferent pupillary defect. In two of these three pairs of eyes, visual acuity was 20/20 in each eye, but the visual field differed considerably between eyes (generalized constriction [mean deviation = -13.32] and inferior arcuate [mean deviation = -8.13] versus a normal field in the fellow eye). In the third pair, there was also a large discrepancy between visual field (superior and inferior arcuate [mean deviation = -13.86] versus normal in the fellow eye), but the visual acuity was also affected (20/40 and 20/15).

A dilated fundus examination was performed on all 92 eyes, and the cup-to-disc ratio was recorded to the nearest tenth. The mean cup-to-disc ratio was 0.11 \pm 0.01. Optic disc appearance is given in Table 3. Seventy-nine (86%) of the optic discs appeared abnormal, but only 42% of these abnormal discs had visible drusen. The remaining abnormal discs were either elevated or had anomalous vasculature. Buried disc drusen were detected among these eyes by B-scan ultrasonography.

Of the 92 eyes, 66 had undergone Humphrey visual field examination, 16 had undergone Goldmann visual field examination, and 10 had undergone both. When both Humphrey and Goldmann perimetry were performed on the same patient, only the Humphrey visual field was analyzed for the purpose of the present study. Visual field defects are given in Table 4. Forty-five (49%) eyes had visual field defects, the large majority being nerve fiber bundle in type. The most common nerve fiber bundle defects were inferonasal sectoral (36%) and inferior arcuate (33%). Nine eyes (20%) had only generalized constriction, and three eyes (7%) had only an increased blind spot.

Visual fields were also analyzed according to appearance of the corresponding optic discs (15) (Table 5). Overall, 73% of optic discs with visible drusen had abnormal visual fields compared with only 36% of optic discs with buried drusen. This difference was statistically significant \((P < 0.05)\).

Humphrey visual field mean deviation and pattern standard deviation were also compared according to the appearance of the corresponding optic discs (Table 6). None of the differences was statistically significant.

**DISCUSSION**

In the present study, we have characterized symptoms and signs associated with visible and buried optic disc drusen. Many of our results are consistent with previous studies (7,8,11,13,14). Our prevalence of drusen at 0.49% is within the described range of 0.34% to 2.4% and actually surpasses the prevalence in some autopsy studies (7,16,17). This higher prevalence may be the result of using ultrasonography in addition to funduscopy.

Visual acuity was well preserved in our patients with an average visual acuity equal to 20/20. The worst visual acuity attributed to optic disc drusen was 20/50. However, approximately one-third of patients described a subjective loss of visual acuity. This was often described as "blurry" or "dim" vision rather than a true visual obscuration. It is difficult to determine whether there was an actual loss of visual acuity without baseline values, but of the 32 patients

<table>
<thead>
<tr>
<th>Optic Disc Appearance</th>
<th>Visual Field Defect</th>
<th>95% confidence interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible drusen</td>
<td>24 (73%)</td>
<td>56.41%–86.61%</td>
</tr>
<tr>
<td>Buried drusen</td>
<td>21 (36%)</td>
<td>24.06%–49.40%</td>
</tr>
<tr>
<td>Elevated/anomalous</td>
<td>15 (33%)</td>
<td>20.41%–44.80%</td>
</tr>
<tr>
<td>Normal disc</td>
<td>6 (46%)</td>
<td>20.28%–75.76%</td>
</tr>
</tbody>
</table>

* Reference 15.
who presented with a complaint of loss of visual acuity, 23 (70%) had visual acuity of 20/20 or better. In 65% of these patients, a visual field defect was present, and it is likely that the patients were interpreting this defect as a loss of visual acuity. Of the patients who complained of visual field loss, 76% had evidence of a defect. There is inherent recall bias in a retrospective study, and these communication difficulties may add to that error when categorizing presenting symptoms. These symptoms may also have been more "specific" if more tests of optic nerve function (such as contrast sensitivity, color vision, and luminance discrimination testing) had been performed. Therefore, we can only conclude that it is common for more than half of patients with optic disc drusen to experience symptoms on presentation.

In our study, 86% of patients had an abnormal-appearing optic disc on funduscopy, but only 42% of those had visible drusen. The other 58% had some combination of disc elevation and anomalous vasculature with buried drusen verified by B-scan ultrasonography. Determining the presence of visible drusen was relatively easy. However, in some cases, it proved difficult to determine whether an optic disc with buried drusen was primarily elevated or anomalous. It was common to have a combination of both characteristics.

The most common visual field defects associated with optic disc drusen in our study were nerve fiber bundle type, the majority in inferonasal sectoral and inferiorarcuate distributions. In contrast to other studies, it appears that we found a lower frequency of enlarged blind spots (7,11). However, we only tabulated enlarged blind spots in the absence of other nerve fiber bundle defects. Had we included a blind spot that extended into an arcuate or sectoral defect, this defect would have been present in approximately 80% of abnormal visual fields.

The most important finding in our study is that visible drusen were associated with a significantly higher proportion of visual field defects than were buried drusen (73% vs. 36%). This difference is similar to that found in previous studies by Mustonen (8) (75% vs. 48%) and Savino et al (11) (71% vs. 25%). However, the strength of our study is that the buried drusen were verified by ultrasonography. These three studies may finally discount theories such as those of Petersen (18), who suggested in 1957 that the "colloid bodies which are deeply embedded in the disc are the ones that are of significance in respect of the visual field." In 1969, Walsh and Hoyt (19) also suggested that "deeply situated drusen lying adjacent to the lamina cribrosa and sclera produce the nerve fiber damage responsible for the visual loss." The fourth edition of their text (20), published in 1982 after the publication of the study by Savino et al (11), stated that "visual field defects in patients with non-swollen, elevated discs without visible drusen are much less common or are milder than those present in patients with visible drusen." We agree with this statement and also with the following statement in the 1998 (fifth) edition of the Walsh and Hoyt text (21): "These results do not rule out the possibility that axonal compression could result from drusen that lie just above the lamina cribrosa rather than those that are superficial and easily seen."

Despite the twofold difference in the frequency of visual defects, we did not find a significant difference in the severity of visual defects caused by visible and buried drusen. There may have been a trend toward a greater mean deviation and pattern standard deviation with visible drusen, but it was not significant in our study. This is in contrast to Mustonen (8) and Kiegl (22), who suggested that superficial disc drusen produce more severe visual field defects.

### REFERENCES


**TABLE 6. Humphrey Visual Field Parameters in Relation to Optic Disc Appearance**

<table>
<thead>
<tr>
<th>Optic disc appearance</th>
<th>n</th>
<th>Mean deviation</th>
<th>P value</th>
<th>Pattern standard deviation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible drusen</td>
<td>26</td>
<td>-5.93 ± 1.10</td>
<td>NA</td>
<td>4.73 ± 0.68</td>
<td>NA</td>
</tr>
<tr>
<td>Buried drusen</td>
<td>50</td>
<td>-4.14 ± 0.68</td>
<td>.151</td>
<td>4.02 ± 0.56</td>
<td>.443</td>
</tr>
<tr>
<td>Elevated/anomalous</td>
<td>39</td>
<td>-4.02 ± 0.62</td>
<td>.110</td>
<td>3.87 ± 0.62</td>
<td>.367</td>
</tr>
<tr>
<td>Normal disc</td>
<td>11</td>
<td>-4.60 ± 2.21</td>
<td>.553</td>
<td>4.52 ± 1.37</td>
<td>.880</td>
</tr>
</tbody>
</table>

NA, not applicable.
Galloping Ophthalmoplegia and Numb Chin in Burkitt Lymphoma

Juan J. Chan Lau, MD, Craig Y. Okada, MD, PhD, and Jonathan D. Trobe, MD

Abstract: A 57-year-old man developed complete bilateral ophthalmoplegia over a period of 10 days, together with bilateral facial pain and numbness of the chin. He had no other clinical manifestations. Findings on brain magnetic resonance imaging and spinal fluid formula from the first lumbar puncture were normal, but cerebrospinal fluid flow cytometry disclosed a kappa restriction monoclonal B-cell population, indicating malignant lymphoma. Computed tomography of the chest, abdomen, and pelvis then revealed multiple enlarged lymph nodes. Biopsy of an inguinal node showed findings consistent with Burkitt lymphoma. Within six weeks, intravenous and intrathecal chemotherapy resolved all neurologic findings except a partial right-side sixth nerve palsy and mild chin numbness. Eighteen months after disease onset, the patient remained in remission. Meningeal spread of Burkitt lymphoma is not commonly a presenting feature in immunocompetent adults. Chin numbness, a characteristic feature caused by infiltration of the mental nerve, should facilitate earlier recognition, which may be life saving.

(J Neuro-Ophthalmol 2004;24:130-134)

Burkitt lymphoma is an aggressive B-cell lymphoma that closely resembles L3 acute lymphocytic leukemia, differing in that the malignant cells in Burkitt lymphoma are found primarily in the lymph nodes rather than in the blood and bone marrow. It was first described in 1958 as a mandibular malignancy in African children (1). Currently, three clinical variations are recognized: 1) an endemic form, often presenting as a mass in the jaw or orbit of African children (1); 2) a nonendemic form, occurring throughout the world and often presenting as an abdominal mass in adults; and 3) an AIDS-associated form, similar to the nonendemic form but clinically more aggressive.

Although diplopia and ocular ductional abnormalities have been previously reported in patients with Burkitt lymphoma, rarely are they the initial manifestations in immunocompetent adults. We present a case in which progressive ophthalmoplegia and numb chin were the presenting manifestations of nonendemic Burkitt lymphoma in an immunocompetent adult with normal findings on brain imaging and spinal fluid formula. In doing so, we emphasize the difficulty yet the urgency of recognizing this neuro-ophthalmic presentation given that timely treatment may be life saving.

Response rates to traditional acute lymphocytic leukemia chemotherapeutic regimens have been dismal, with a complete response rate of 44% to 63% and a disease-free survival of 0% to 50%. However, newer intensive treatment regimens offer significantly better clinical outcomes (2,3). With multiagent intensive chemotherapy and aggressive early intrathecal treatment, complete responses can be obtained in 60% to 86% of treated patients, with 50% to 70% having a sustained disease-free survival (2-4). Patients with increased tumor bulk and widely disseminated disease have lower response rates and a higher risk of relapse (2,5). Moreover, the development of a life-threatening acute tumor lysis syndrome is more severe with increased tumor burden.

CASE REPORT

A 57-year-old man without ongoing health problems or constitutional symptoms developed double vision. An ophthalmologist diagnosed a right sixth cranial nerve palsy. Two days later, he developed complete right upper lid ptosis, and four days later, he awoke with severe paroxysmal pain radiating from the right preauricular region to the right side of the chin. Within a day, he had developed persistent marked numbness of the right side of the chin. Within a day, he had developed persistent marked numbness of the right side of the chin.

Findings on a brain computed tomography (CT) scan and magnetic resonance imaging (MRI) with gadolinium were normal. Because of bradycardia, a pacemaker was implanted. Several days later, he developed paroxysmal pain of the left eye, brow, scalp, and mouth. He was transferred to our care.

His past medical history included hepatitis B antigenemia detected 10 years earlier without manifestations of
liver disease. His only medication was 12.5 mg rofecoxib twice a day for osteoarthritis.

The general physical examination was normal, including vital signs. Neuro-ophthalmologic examination showed normal visual function. There was complete right upper lid ptosis, total immobility of the right eye, and a 7-mm unreactive right pupil. The left eye had 0% abduction, 60% adduction, and normal vertical ductions. The 4-mm left pupil reacted normally to direct light. Corneal sensation was intact bilaterally. There was markedly reduced pinprick sensation over the right chin region. There was reduced pinprick sensation over the left side of the scalp and brow extending to the interaural line and involving, to a lesser extent, the left side of the chin. All other aspects of the neurologic and ophthalmologic examinations were normal.

Within three days of our initial examination, he had developed total bilateral ophthalmoplegia, complete right ptosis, partial left ptosis, bilateral 7-mm pupils unreactive to direct light or a near target, and bilateral chin hypesthesia. A white blood cell count was $10.8 \times 10^3$ cells/mm$^3$, hemoglobin was 13.7 g/dL, and platelet count was $293 \times 10^3$ cells/mm$^3$. A high-resolution brain CT scan was normal. (The MRI scan performed earlier was reviewed carefully and showed no abnormalities, as originally described. A repeat MRI scan could not be performed because of his new pacemaker.) Lumbar puncture revealed the following values: an opening pressure of 120 mm H$_2$O; glucose, 64 mg/dL; protein, 69 mg/dL; red blood cell count, 98 cells/µL; white blood cell count, 2 cells/µL; and negative cryptococcal antigen and VDRL test results. Cytospin preparations of the cerebrospinal fluid (CSF) did not show any malignant-appearing cells. However, flow cytometry of the CSF lymphocytes showed a kappa restricted population of B cells. Computed tomography scan of the chest, abdomen, and pelvis showed multiple low-density liver abnormalities, enlarged lymph nodes in all three regions, and diffuse, hazy stranding in the mesentery and omentum (Fig. 1), findings suggestive of non-Hodgkin lymphoma. Histologic study of an excised large, right inguinal lymph node showed a characteristic “starry sky” pattern consistent with the diagnosis of the Burkitt variant of lymphoma (Fig. 2). Cytogenetic analysis of bone marrow aspirate confirmed the diagnosis with the disclosure of the t(8,14) c-myc translocation. Cerebrospinal fluid from a lumbar puncture performed 12 days following the original lumbar puncture contained 230 g/dL protein and 42 white blood cells/mm$^3$ with 98% lymphocytes. Cytospin preparation of the CSF leukocytes showed cells of Burkitt lymphoma (Fig. 3).

He was started on the CALGB 9251 chemotherapy regimen. Cycle 1 (prephase), consisting of 1 g intravenous methylprednisolone daily and cyclophosphamide for five days, produced no change in the neuro-ophthalmic manifestations. This was complicated by tumor lysis syndrome and renal failure that required hemodialysis. He then began cycle 2 chemotherapy shortly after his prephase treatment, which consisted of ifosfamide, MESNA, Ara-C, and dexamethasone. He was also treated with intrathecal methotrexate, Ara-C, and hydrocortisone. Within six weeks of starting chemotherapy, his ophthalmic abnormalities had resolved except for mild chin numbness and a mild abduction deficit in the right eye. In primary gaze, his eyes became aligned. On a follow-up visit at 12 months after the initiation of chemotherapy, he remained in clinical and hematological remission.

**DISCUSSION**

Over a period of 10 days, our patient developed complete bilateral ophthalmoplegia, ptosis, and mydriasis, together with paroxysmal facial pain and chin numbness. Brain CT and MRI scans were normal, but flow cytometry of CSF showed a monoclonal B-cell population. Aggressive chemotherapy rapidly resolved nearly all neurologic manifestations and placed him in complete remission. This patient is unusual in that ocular motor palsy caused by imaging-negative meningeal infiltration of cranial nerves in Burkitt lymphoma have not been previously documented as the presenting features in an immunocompetent host.
FIG. 2. Right inguinal lymph node with monotonous proliferation of intermediate-sized lymphoid cells with a high mitotic rate. The "starry sky" pattern of the biopsy is due to numerous macrophages that are ingesting apoptotic tumor cells. The macrophages are called "tingible body macrophages" because they are filled with dark-staining nuclear debris and lighter-staining lipids.

Grassi and Lee (6) reported a 53-year-old human immunodeficiency virus (HIV)-positive man who presented with a severe headache and diplopia. Examination disclosed partial third, fifth, sixth, and seventh cranial nerve palsy. Magnetic resonance imaging showed diffuse meningeal enhancement. CSF flow cytometry disclosed a monoclonal B-cell population consistent with Burkitt lymphoma. He died within 30 days of diagnosis because of a lymphomatous pericardial effusion. Snider et al (7) reported two patients with AIDS and Burkitt lymphoma who presented with diplopia. One patient had unilateral third and sixth nerve palsies, bilateral seventh nerve palsies, right arm weakness, areflexia, and bilateral chin numbness; the other patient had unilateral third and seventh nerve palsies, four-limb weakness, and areflexia. Cerebrospinal fluid cytologic findings were positive in both, but only after the third lumbar puncture in one patient and after the second lumbar puncture in the other. One patient died shortly thereafter of sepsis; the outcome of the other patient was not specified.

Unlike immunoblastic lymphomas, Burkitt lymphoma arising in HIV-positive patients occurs at a time when such patients are not yet seriously immunocompromised (2). Although Burkitt lymphoma is less responsive to treatment in HIV-positive patients, Spina et al (8) found no difference in the clinicopathologic features in patients with and without HIV. The authors described meningeal involvement in 9 (19%) of 46 HIV-positive patients and in 5 (17%) of 29 HIV-negative patients ($P = 0.8$).

Newman et al (9,10) reported a case similar to ours, except that the patient was immunocompromised by medications following a liver transplant. Their patient was a 58-year-old man who complained of right lower facial pain that was followed by right hand weakness and horizontal binocular diplopia. Examination showed a right mental neuropathy, a right sixth nerve palsy, and weakness of the right arm. Five days later, he manifested complete bilateral third and sixth cranial nerve palsy. Corneal and facial sensation were normal except for mildly decreased sensation on the right side of the chin. Neuroimaging, CSF analysis, total body CT scanning, and a paraspinal biopsy revealed no abnormalities. However, sural nerve biopsy disclosed a lymphoid infiltration of the perivascular endoneurium. Burkitt lymphoma was diagnosed by bone marrow biopsy. The patient was treated aggressively with intravenous and intrathecal chemotherapy. At a 10-month follow-up visit, he still had, like our patient, a mental neuropathy and a mild left sixth nerve palsy (10).

Previously reported immunocompetent patients with diplopia and Burkitt lymphoma have all had discrete intraorbital or intracranial tumor masses noted on imaging. For example, Inoue et al (11) reported a 58-year-old immunocompetent man who had diplopia as the initial manifestation of Burkitt lymphoma secondary to tumor infiltration of the medial rectus muscle. Coupland et al (12) reported a 84-year-old immunocompetent woman with diplopia as the first clinical manifestation of a large orbital Burkitt lymphoma. Trese et al (13) described Burkitt lymphoma in an immunocompetent 22-year-old man whose initial finding on brain imaging was negative, but sino-orbital masses appeared within four weeks of presentation. He presented with painless horizontal diplopia caused by a left sixth

![FIG. 3. Cytospin preparation of cerebrospinal fluid shows four Burkitt lymphoma cells. A normal red blood cell and lymphocyte are included for size comparison.]
nerve paresis. The finding on lumbar puncture was negative. Within four weeks, he had developed a mild left seventh nerve palsy, decreased left corneal sensation, a right sixth nerve palsy, and, eventually, complete bilateral internal and external ophthalmoplegia, together with bilateral first and second division trigeminal neuropathy. Neuroimaging studies showed masses in both ethmoid sinuses extending into the sphenoid sinuses, right orbit, and right olfactory groove. Biopsy was consistent with Burkitt lymphoma. A repeat lumbar puncture showed cells consistent with Burkitt lymphoma. Chest x-ray showed a pathologic fracture of the left third rib with an extrapleural mass. The ophthalmoplegia gradually improved during a six-week course of chemotherapy, but the right sixth nerve palsy persisted. The patient died of sepsis within three months of diagnosis. At postmortem examination, no tumor was found within the CSF spaces, brain parenchyma, orbits, or ethmoid or sphenoid sinuses.

The combination of rapidly progressive ophthalmoplegia and chin numbness signals the presence of an aggressive cancer. Although it may be caused by dental anesthesia, sagittal split osteotomies, and trauma (14,15), nontraumatic "nomb chin syndrome" (NCS) is most commonly a sign of neoplastic infiltration of the mental canal, particularly by malignant lymphoma or breast cancer (14,16). The original description of NCS in 1830 by Charles Bell involved an elderly woman with metastatic breast cancer (17). Subsequently, numb chin syndrome has been reported in acute leukemia; in colon, lung, nasopharyngeal, ovarian, prostate, and lip cancer; and in hypernephroma, melanoma, and multiple myeloma (14,16,18-27). Massey et al (19) reported chin numbness in 19 patients; 9 of the 19 patients had lymphoreticular malignancies, one of which was Burkitt lymphoma.

The clinical presentation of NCS is usually with dysesthesias or numbness extending from the chin to the lower lip and an abnormal sensation of thickening of the lower lip. Numb chin syndrome is usually unilateral but may be bilateral (16), as in our case. Massey et al (19) found that it preceded the diagnosis of malignancy in nearly half of cases. By contrast, Lossos and Siegal (16) found NCS to be a late manifestation of systemic malignancy, with a median latency of 2.5 years after diagnosis of lymphoproliferative neoplasm and four years after diagnosis of breast cancer. In 67% of the patients, NCS arose in association with progression of the disease, whereas in 31% it heralded a relapse (16). In the series of Massey et al (19), plain jaw x-rays showed lytic or blastic lesions in only one-third of patients tested. Chemotherapy or radiotherapy resolved the numbness in three-fourths of patients.

Flow cytometry played a critical role in the diagnosis of Burkitt lymphoma in our patient. The ability to detect malignant cells, the presence of nonmalignant cells that obscure rare malignant cells, or the presence of reactive lymphocytes that mimic the appearance of tumor cells. In our case, analysis of the CSF did not reveal a significant leukocytosis, and results of cytologic evaluation of the CSF lymphocytes were negative for malignant cells. However, flow cytometric analysis of the CSF suggested a malignancy. Flow cytometry measures the surface expression of cell lineage-specific protein at a single cell level. A population of normal B lymphocytes expresses either kappa or lambda immunoglobulin light chains, whereas a population of malignant B lymphocytes expresses only kappa or lambda light chains. Flow analysis of CSF from our patient revealed that the vast majority of the B cells expressed kappa immunoglobulin light chains, indicating a malignant process. The addition of flow cytometric analysis to morphologic examination of CSF lymphocytes has increased the detection rate of lymphoid neoplasms by 43% to 75% (28-30). This technique should be used to analyze CSF lymphocytes whenever a malignancy is suspected and there are at least 2 lymphocytes/mm<sup>3</sup> in the CSF. Collection of 10 mL or more CSF on multiple occasions may be necessary to obtain an adequate sample.

REFERENCES

Concurrent Sino-Orbital Aspergillosis and Cerebral Nocardiosis

Liselotte Pieroth, MD, Jacqueline M. S. Winterkorn, MD, PhD, Hermann Schubert, MD, William S. Millar MD, MS, and Michael Kazim, MD

Abstract: A 79-year-old man with myelodysplastic syndrome developed a right optic neuropathy with optic disc edema and intractable periocular pain, one month after undergoing removal of a gangrenous gallbladder. Although results of a temporal artery biopsy were negative, he was treated with prednisone for presumed temporal arteritis. Attempts at tapering the prednisone dose led to recurrence of periocular pain. On neuro-ophthalmologic evaluation six months after the prednisone treatment was begun, he had developed right fourth and sixth cranial nerve palsies, and...
magnetic resonance imaging demonstrated a right orbital apex mass. Trans-sphenoidal biopsy revealed Aspergillus fumigatus. During treatment of aspergillosis, the patient developed a left hemiparesis. Magnetic resonance imaging disclosed multiple ring-enhancing cerebral masses. Biopsy revealed Nocardia asteroides. The patient was successfully treated for both infections with recovery of neurologic function except for the right optic neuropathy. Although immunocompromised patients are known to be subject to multiple infections, this may be the first reported case of concurrent sino-orbital aspergillosis and cerebral nocardiosis.

(J Neuro-Ophthalmol 2004;24: 135–137)

A 79-year-old man suddenly lost vision in his right eye and developed right periocular pain one month after he underwent cholecystectomy for a gangrenous but culture-negative gall bladder. Visual acuity was hand movements OD, 20/25 OS. The right optic disc was swollen, the left optic disc was normal. These findings suggested anterior ischemic optic neuropathy. He had previously been diagnosed with a myelodysplastic disorder characterized by anemia and thrombocytopenia. Westergren erythrocyte sedimentation rate was 86 mm/h. No brain imaging was performed. Despite negative findings on temporal artery biopsy, he received a presumptive diagnosis of temporal arteritis and was treated with 60 mg/d prednisone, which eliminated his pain. Each time the prednisone was tapered to 40 mg, pain recurred, so the dose was maintained at 60 mg/d.

Six months after commencement of prednisone treatment, he was referred for neuro-ophthalmologic evaluation. Visual acuity was no light perception OD, 20/40 OS. Right fourth and sixth cranial nerve palsies were observed, localizing the lesion to the right orbital apex. Magnetic resonance imaging (MRI) showed an enhancing mass in the right orbital apex, optic foramen, and adjacent anterior clinoid, with a component in the sphenoid sinus (Fig. 1A). Lumbar puncture opening pressure was 140 mm H₂O, with a normal cell count and normal protein and glucose values. Fungal and bacterial cultures of cerebrospinal fluid and blood were negative. Endoscopic biopsy of the mass was performed by the trans-sphenoidal approach. Gomori methenamine silver stain revealed the septate hyphae of Aspergillus fumigatus (Fig. 1B).

The patient was treated for invasive aspergillosis with 250 mg intravenous liposomal amphotericin daily. Vision did not recover. Three months later, he developed a left hemiplegia. MRI revealed multiple new ring-enhancing lesions in the cerebrum (Fig. 2A). Biopsy of a right frontal cortex lesion disclosed Nocardia asteroides (Fig. 2B). The patient was treated with 200 mg intravenous minocycline and 500 mg intravenous imipenem daily. Six months later, his neurologic status had normalized, apart from a persisting right optic neuropathy. A repeat MRI scan six months after treatment showed no cerebral lesions. However, the orbital mass persisted. He died of pneumonia two years after the onset of the optic neuropathy.

Immunocompromised patients are particularly susceptible to infections of the paranasal sinuses, yet multiple infections have rarely been reported. Our patient, immunocompromised by a myelodysplastic disorder, developed invasive aspergillosis originating in the right sphenoid sinus and extending into the orbital apex and cavernous sinus, causing optic neuropathy and ophthalmoplegia. Hematogenous spread of invasive aspergillosis from the gastrointestinal tract has also been reported (1,2). Optic neuropathy resulting from invasive aspergillosis may initially manifest as optic neuritis or ischemic optic neuropathy (3–5). In the present case, the swollen disc led to the misdiagnosis of temporal arteritis. The optic neuropathy of aspergillosis may initially improve with corticosteroid treatment, but ultimately the organisms proliferate and cause further damage, as occurred in our case (5,6). Invasive aspergillosis can occlude cerebral vessels (7,8) and cause cerebral infarcts, but our patient’s hemiplegia was due to a second infection by N. asteroides.

N. asteroides is an aerobic, gram-positive, filamentous bacterium with a branching growth pattern. Ring-enhancement on MRI is characteristic of nocardial infection. Although concomitant pulmonary infections occur commonly, dual infections have been documented in only a few immunocompromised patients (9–12). Concurrent cerebral infection has occurred from toxoplasmosis and cytomegalovirus or cryptococcus, and cerebral aspergillosis with candidiasis. To our knowledge, the case presented in the current report is the first reported case of sino-orbital aspergillosis concurrent with cerebral nocardiosis.

REFERENCES


Idiopathic Intracranial Hypertension

Deborah I. Friedman, MD and Daniel M. Jacobson, MD

Abstract: The syndrome of intracranial hypertension without structural brain or cerebrospinal fluid abnormalities and without identifiable cause, now most appropriately termed idiopathic intracranial hypertension, was described over a century ago. Although the pathogenesis of this condition remains unknown, diagnostic and therapeutic developments during the past two decades have substantially advanced patient management.


DEFINITION

The syndrome of increased intracranial pressure (ICP) without ventriculomegaly or mass lesion, and with normal cerebrospinal fluid (CSF) composition, was first described more than a century ago, yet we still know little about its pathogenesis (1). Often referred to as "pseudotumor cerebri" but more appropriately called "idiopathic intracranial hypertension" (IIH), it is a surprisingly common disorder. In young overweight women, the annual incidence is as high as 20 per 100,000 persons (2).

The definition of IIH has evolved with clinical experience and advances in imaging technology. Currently, IIH can be diagnosed only if the following criteria are met (Table 1): 1) symptoms and signs attributable to increased ICP or papilledema; 2) elevated ICP recorded during lumbar puncture in the lateral decubitus position; 3) normal CSF composition; 4) no imaging evidence of ventriculomegaly or a structural cause for increased ICP, such as a brain parenchymal, ventricular, meningeal, or venous sinus abnormality; and 5) no other cause of intracranial hypertension identified, such as use of certain medications.

The diagnosis and management of IIH remains based largely on anecdotal evidence. However, substantial developments during the past two decades have provided clinicians with more tools for excluding disorders that mimic IIH and for facilitating its diagnosis and management.

NOMENCLATURE

The nomenclature for IIH remains controversial. "Benign intracranial hypertension" is no longer accepted, as significant visual morbidity may occur with this disorder (3). The term "pseudotumor cerebri," a historically popular and all-encompassing term, leaves the impression that IIH is not a real disease. IIH is currently the favored term for the primary (idiopathic) disorder. For those patients with an identified cause of intracranial hypertension without structural brain imaging or CSF constituent abnormalities, the appropriate diagnostic term would be "intracranial hypertension secondary to (...)." The typical patient with IIH is an obese woman of childbearing age (4). Atypical patients include men, slim women, prepubescent children, and patients older than age 44 years.

NATURAL HISTORY AND VISUAL PROGNOSIS

There are few prospective data in the era of modern imaging (computed tomography [CT], magnetic resonance imaging [MRI], and magnetic resonance venography [MRV]) to document the natural history of the disorder. Clinical experience, however, suggests that it is common for patients to have a protracted course lasting months to years, during which they may be asymptomatic but have chronic papilledema, or have symptoms that require medical agents to lower their ICP. This suggests that intracranial hypertension, symptomatic or not, persists in many patients with IIH. Indeed, one series found that 10 (83%) of 12 patients in long-term follow-up who underwent repeated lumbar punctures showed persistently elevated ICPs ranging from 220 to 550 mm H₂O (5). Recurrent symptoms and papilledema have been reported in 8% to 37% of patients often years after the initial diagnosis (5,6).

The principal morbidity of IIH is papilledema-associated visual loss. A prospective study of 50 patients with IIH found visual field defects at initial presentation in at least one eye in 96% of patients assessed with the Goldmann perimeter, and in 92% of patients assessed with the Humphrey perimeter (4). After treatment, 60% of patients improved, 30% remained stable, and 10% worsened, as assessed with Goldmann perimeter (4). Assessed with the Humphrey perimeter, 50% of patients improved, 28% remained stable, and 22% worsened (4).
Idiopathic Intracranial Hypertension

Trary to popular belief, there is no evidence that body weight normal, and 201 to 249 mm H\textsubscript{2}O is nondiagnostic (9). Con­
mum CSF opening pressure required for diagnosing IIH. In	
times conflicting, recommendations regarding the mini­
tional MRV for detecting areas of subtle cerebral venous	
Using a special technique, three-dimensional gadolinium-
reduced ICP. More certain, and likely reflects a compensatory response to in­
cerebral venous thrombosis, may mimic IIH yet not have	
underlying condition. Accordingly, this imaging technique	
that increase ICP without producing ventriculomegaly or	
ventriculomegaly or a mass lesion. However, conditions	
increase ICP without producing ventriculomegaly or mass lesions, such as gliomatosis cerebri, meningitis, and	
cerebral venous thrombosis, may mimic IIH yet not have associated CT abnormalities to provide a clue to the true underlying condition. Accordingly, this imaging technique may be suboptimal, particularly for atypical patients. Un­less there are external constraints (weight limitations, avail­ability), MRI with MRV is currently the study of choice. Using a special technique, three-dimensional gadolinium-
enhanced MRV appears to be more sensitive than conven­tion MRV for detecting areas of subtle cerebral venous stenosis (8). The clinical relevance of these changes is uncertain, and likely reflects a compensatory response to in­creased ICP.

TABLE 1. Clinical criteria for diagnosing idiopathic intracranial hypertension*  

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Note</th>
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<tbody>
<tr>
<td>Symptoms, if present, represent increased intracranial pressure or papilledema</td>
<td>Documented elevated intracranial pressure during lumbar puncture measured in the lateral decubitus position</td>
</tr>
<tr>
<td>Signs represent increased intracranial pressure or papilledema</td>
<td>Normal cerebrospinal fluid composition</td>
</tr>
<tr>
<td>Documented elevated intracranial pressure</td>
<td>No evidence of ventriculomegaly, mass, structural, or vascular lesion on magnetic resonance imaging or contrast-enhanced computed tomography for typical patients, and magnetic resonance imaging and magnetic resonance venography for all others</td>
</tr>
<tr>
<td>Normal cerebrospinal fluid composition</td>
<td>No other cause (including medication) of intracranial hypertension identified</td>
</tr>
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* Adapted from reference 7.

DIAGNOSIS

Imaging

With advances in neuroimaging techniques and a growing understanding of the pathophysiology of IIH, the diagnostic criteria for this condition have recently been revised (7) (Table 1). A noncontrast CT was previously con­sidered an adequate imaging study because it can exclude ventriculomegaly or a mass lesion. However, conditions that increase ICP without producing ventriculomegaly or mass lesions, such as gliomatosis cerebri, meningitis, and cerebral venous thrombosis, may mimic IIH yet not have associated CT abnormalities to provide a clue to the true underlying condition. Accordingly, this imaging technique may be suboptimal, particularly for atypical patients. Un­less there are external constraints (weight limitations, avail­ability), MRI with MRV is currently the study of choice. Using a special technique, three-dimensional gadolinium-enhanced MRV appears to be more sensitive than conven­tion MRV for detecting areas of subtle cerebral venous stenosis (8). The clinical relevance of these changes is uncertain, and likely reflects a compensatory response to in­creased ICP.

CSF Opening Pressure

The medical literature contains various, and some­times conflicting, recommendations regarding the mini­mum CSF opening pressure required for diagnosing IIH. In
general, however, a CSF pressure greater than 250 mm H\textsubscript{2}O is consistent with the diagnosis, less than 200 mm H\textsubscript{2}O is normal, and 201 to 249 mm H\textsubscript{2}O is nondiagnostic (9). Con­trary to popular belief, there is no evidence that body weight influences these cutoff values. The upper limit of normal CSF pressure in children is generally considered to be 180 to 200 mm H\textsubscript{2}O; the effect of obesity in children has not been studied.

Visual Fields

Although visual acuity and color perception are generally preserved in papilledema unless it enters a chronic and atrophic stage (10-12), visual fields and contrast sensi­tivity may be abnormal earlier. Visual field testing is far more sensitive for detecting optic nerve damage producing visual loss, particularly in the early stages of the disorder. Quantitative perimetry with static or kinetic methods is the current standard for assessing visual fields in IIH. The sensi­tivity to the detection of visual field defects is similar us­ing either technique, assuming an experienced perimetrist performs the kinetic test (11,13).

Newer perimetric techniques, such as frequency­doubling technology perimetry, short-wavelength auto­mated perimetry, tendency-oriented perimetry, and high-pass resolution (ring) perimetry have been examined in pa­tients with glaucoma, but, with the exception of high-pass resolution perimetry (14), not well-studied in other optic neuropathies or in IIH. Motion perimetry, in which computer graphics generate small circular regions of coherent motion perception targets throughout the central visual field, identified the visual field defects in patients with IIH detected with conventional automated perimetry, as well as some defects that were not identified using automated perimetry (15). These results, and those elicited with other newer perimetric techniques, must be confirmed and vali­dated before the newer tools replace the current visual field testing methods.

Monitoring the Optic Nerve Head

Whereas the results of visual field testing provide functional information concerning the degree of optic nerve damage, assessment of the degree of papilledema change over time often provides a useful structural measure of the clinical course and effect of treatment. In some patients, however, papilledema never resolves completely despite resolution of symptoms and stabilization of visual function. It is important to document the appearance of the optic disc with photographs, ideally at the first evaluation and whenever there is a change.

Confocal scanning tomography is a new tool that can quantify the degree of papilledema and measure changes over time (16). Tomographic parameters of the optic nerve head seem to correlate with visual field sensitivity loss (17). For routine patient care, however, confocal scanning tomography is not a practical tool and may not provide more useful information than carefully performed and interpreted visual fields. Future studies are needed before deciding if this technique will find a place in routine patient management.
Visual Acuity

Loss of visual acuity generally does not occur in acute papilledema unless there is macular edema. As untreated papilledema becomes more chronic, however, progressive impairment of visual acuity can be expected from a variety of causes (Table 2).

Contrast Sensitivity

Loss of contrast sensitivity is frequently identified in patients with IIH, regardless of the technique used (10-12). For that reason, some investigators recommend contrast sensitivity testing as an adjunctive measure to assess optic nerve function. Whereas this tool may detect a global abnormality of optic nerve function when other standard measures are normal (11), its specificity for optic nerve dysfunction is low.

Visual Evoked Potentials

Assessment of visual evoked potentials (VEP) is often performed to screen for injury to the optic nerve. However, this technique probes only the central 10 degrees of visual field, a region that is insensitive to visual loss in papilledema (11). Thus, there is no role for VEP in evaluating patients with IIH. The future role of multifocal VEP, which is capable of assessing nonfoveal neurotransmission, remains to be determined.

RISK FACTORS FOR VISUAL LOSS

Several clinical series have identified factors that may influence visual outcome in patients with IIH (Table 3) (2,18-22). The reliability of these variables in clinical practice may be limited on an individual case basis because they were determined from retrospective studies. Some reports provide conflicting results.

<table>
<thead>
<tr>
<th>TABLE 3. Predictors and nonpredictors of visual loss in patients with idiopathic intracranial hypertension*</th>
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<tr>
<td>Factors predictive of visual loss</td>
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<tr>
<td>Recent weight gain</td>
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<td>High-grade papilledema</td>
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<td>Atrophic papilledema</td>
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<td>Subretinal hemorrhage</td>
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<tr>
<td>Significant visual field loss at presentation</td>
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<td>Hypertension</td>
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<tr>
<td>Factors not predictive of visual loss</td>
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<tr>
<td>Duration of symptoms</td>
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<td>Transient visual obscurations</td>
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<tr>
<td>Double vision</td>
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<td>Pulsatile intracranial noises</td>
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<td>Degree of headache</td>
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<tr>
<td>Opening pressure during lumbar puncture</td>
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<tr>
<td>Pregnancy</td>
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* Adapted from references 2, 17-21.

MIMICKERS OF IIH

As long as the diagnostic guidelines outlined in Table 1 are followed, there is little chance of failing to diagnose an ominous mimicker of IIH. Still, some cases of cerebral venous sinus thrombosis, gliomatosis cerebri, and leptomeningeal infiltration by a chronic neoplastic or infectious process may escape detection with brain imaging and CSF analysis until late in their course. Red flags that should signal the possible presence of a mimicker are outlined in Table 4 (23-26).

One should be particularly cautious about falsely diagnosing IIH in patients with abnormal visual fields that are psychogenic in nature, in those with anomalous optic discs, and when the opening pressure during lumbar puncture was improperly measured. Because concentric visual field constriction is a finding common to both psychogenic visual loss and IIH, misinterpretation of this visual field defect is a particularly frequent problem (5).

TREATMENT

Indications for Treatment

Not all patients with IIH require treatment. After establishing the diagnosis, asymptomatic individuals with

<table>
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<tr>
<th>TABLE 4. “Red flags” that suggest the presence of a mimicker of idiopathic intracranial hypertension</th>
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<tr>
<td>Atypical demographic profile</td>
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<tr>
<td>Cranial nerve palsies other than sixth nerve palsy</td>
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<tr>
<td>Alteration in level of consciousness</td>
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<td>Focal neurologic signs apart from sixth nerve palsy</td>
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<tr>
<td>Abnormal CSF profile (low glucose or high protein concentrations)</td>
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<tr>
<td>Explosive onset of symptoms</td>
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<tr>
<td>Rapid development of visual loss and progression of symptoms</td>
</tr>
<tr>
<td>Global optic atrophy</td>
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<tr>
<td>Internuclear ophthalmoplegia</td>
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<td>Vertical gaze disorder</td>
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normal vision and minimal papilledema can be monitored frequently for the development of symptoms or visual decline. A small percentage of patients improve after their diagnostic lumbar puncture (LP). The reason for the apparent cure is uncertain and may relate to re-establishing normal CSF homeostasis or cerebral venous pressure when normal CSF pressure is temporarily restored (27). Patients experiencing transient visual obscurations with normal visual function may be observed unless they have moderately severe papilledema. Some patients with headaches and minimal visual signs (visual field loss limited to a slightly enlarged blind spot) may also be managed conservatively.

Therapy is initiated in the presence of visual acuity or visual field loss apart from mild enlargement of the blind spot, moderate to severe (Frisen grade 3–5) papilledema or persistent headaches (28). Visual signs and symptoms often co-exist with headache, but the two manifestations are approached independently. Treatment is always indicated when patients are aware of their visual deficit.

Dietary Management

Dietary management and weight loss are time-honored treatments, supported by several observational studies (29–36). The earliest report described rapid resolution of papilledema in nine obese patients treated with a very low-caloric (400–1,000 calories daily) rice diet (29). One retrospective study correlated weight loss to papilledema in 15 women with IIH who were treated with acetazolamide at the time of diagnosis (30). Within the 24-week study period, 11 patients had improvement or resolution of papilledema. The six patients who had complete resolution of marked papilledema underwent a mean weight loss of 6.2% total body weight. Patients who were unable to achieve the same degree of weight loss had lesser degrees of improvement in their papilledema grade. The four patients with unchanged optic disc swelling had no weight loss during the study period.

Another retrospective series evaluated the effect of weight loss on visual function and papilledema grade in 58 patients (31). There was more rapid improvement in papilledema and visual fields in overweight women with IIH who lost weight (mean weight loss 13.3 ± SD 9.9 lb) than in those who did not lose weight (mean weight loss 0 ± SD 0.6 lb). Surgically induced weight loss (mean loss 57 ± 5 kg) was associated with decreased CSF pressure and resolution of papilledema in eight patients examined 34 ± 8 months postoperatively (32). Various procedures used over the 11-year study period included horizontal gastroplasty, vertical banded gastroplasty, proximal Roux-en-Y gastric bypass, and distal gastric bypass.

There is little scientifically robust information regarding specific dietary measures for IIH. Limiting vitamin A consumption and a low tyramine diet may be beneficial (33–36). Dietary sources rich in vitamin A include fish, eggs, carrots, sweet potatoes, leafy greens, broccoli, red bell peppers, tomatoes, apricots, and cantaloupe. Supplemental vitamin A preparations are available over-the-counter. Tyramine naturally accumulates in food during the aging process. Foods and beverage that have high tyramine content include aged cheese and meat, pickled foods, overripe or dried fruit, beer, and wine. As many of the high-tyramine foods are also migraine triggers, patients may be instructed to use resources that are available to migraineurs regarding diet.

Repeated Lumbar Punctures

Repeated LPs are sometimes used in patients with occasional symptom relapses, in pregnant women, or in the setting of rapidly declining vision to temporarily lower the CSF pressure while planning a more aggressive treatment. However, the procedure may be painful, technically difficult to perform, and cause a low-pressure headache (37). Other complications of LP, such as infection, tonsillar herniation, radiolucent, and arachnoiditis, are rare. Considering that 50 mL of CSF are produced in a day in humans at a rate of approximately 0.35 mL/min, 20 mL of CSF removed by LP is replenished in one hour, provided there is no persistent CSF loss through the dural puncture site or alteration in CSF production caused by the LP (38).

Carbonic Anhydrase Inhibitors

Acetazolamide is generally accepted as a first-line medication for lowering the intracranial hypertension in patients with IIH. Its carbonic anhydrase inhibition decreases the secretion of CSF by the choroid plexus. Doses of 1 to 2 g are generally used and some advocate increasing to the maximum tolerated dose if necessary. Side effects are common but are better accepted when patients are aware of their potential occurrence and medication doses are built up gradually. Alternatively, methazolamide may be used but it has no particular therapeutic advantage over acetazolamide. Topiramate, an anti-epileptic medication with carbonic anhydrase inhibitory properties, may prove to be useful for IIH, particularly because it is also useful for headache prophylaxis and often produces weight loss (39). Currently, treatment of IIH with topiramate has not been studied and is considered off-label usage.

Other Diuretics

Furosemide also has beneficial effects on CSF secretion and may be used (39). Other diuretics are used but no consistent therapeutic trend has been reported. Most diuretics contain a sulfa moiety that may be problematic in patients who are allergic to sulfa. Triamterene and spironolactone are useful in this circumstance, although they have no proven effect on CSF production.
Corticosteroids

Corticosteroids are not advocated for routine or long-term management of IIH. They are useful as an adjunctive treatment in patients with rapid deterioration while arranging a surgical procedure (see "malignant" IIH) (40). Withdrawal of corticosteroids may lead to a rebound increase in ICP (41,42). Moreover, their side effects (weight gain, fluid retention, hyperglycemia) are problematic in IIH patients.

Management of Headaches

The chronic headaches of IIH are best treated with conventional headache prophylaxis, although in some cases lowering the ICP with medical methods is effective (37). Because of the potential dangers, we do not advocate CSF shunting procedures for headache alone. At the same time, many of the agents used for headache prophylaxis in IIH (tricyclic antidepressants, selective serotonin reuptake inhibitors, sodium valproate, calcium channel blockers) may produce weight gain or edema that is undesirable in this population. Many patients with IIH also have migraine, tension-type headaches, or analgesic overuse headaches (43). Headache prevention is recommended in IIH as long as the patient is monitored for medication-induced weight gain (43).

Medical treatment of IIH is seldom life-long. When the patient's visual status and optic nerve appearance have stabilized, or when the disease has been in remission for at least six months, ICP-lowering agents may be tapered and discontinued. Patients should still be periodically monitored at this point because recurrences are not rare. Weight gain is associated with recurrence in some patients (44). Recurrence of symptoms may warrant reinstitution of medications but headaches are typically managed without diuretics or carbonic anhydrase inhibitors unless there is evidence of elevated ICP.

SURGICAL TREATMENT

Surgery is considered under the following circumstances: 1) progressive loss of vision despite maximal medical therapy; 2) severe or rapid visual loss at onset (see "malignant IIH"), including the development of an afferent pupillary defect or signs of advancing optic nerve dysfunction; and 3) severe papilledema causing macular edema or exudates (37,45).

Surgical procedures used for the treatment of visual loss include optic nerve sheath decompression (ONSD) and CSF diversion procedures. Whether one procedure is superior to the other is controversial and the decision often depends on available resources and expertise. The success rate is comparable between ONSD and lumboperitoneal shunt (46). Advantages of ONSD are shorter anesthesia and hospitalization times. ONSD avoids the complications of shunting (Table 6). Approximately 50% of patients experience improvement in the nonoperated eye after a single ONSD (47).

Optic Nerve Sheath Decompression

The mechanism by which ONSD benefits IIH is uncertain. One possibility is a filtering effect with local CSF pressure reduction improving the peripapillary circulation (47). A second possibility is a generalized decrease in ICP, which has been demonstrated after ONSD (48,49). A third possibility is that scarring of the arachnoid after the procedure may protect the nerve head from the elevated CSF pressure. ONSD in monkeys produces connective tissue proliferation and obliteration of the subarachnoid space near the area of operation (50); similar changes were found in one human postmortem study (51).

The complication rate of ONSD ranges broadly from 4.8% to 45%, with a mean of 12.9% (52–62). Meta-analysis is difficult because there are so many variables, including the surgical approach (medial versus lateral), surgical experience, duration of follow-up, criteria for an event to be considered a complication, and primary procedure versus reoperation. Complications of ONSD are listed in Table 5.

In a review of 317 published cases by Anthony Arnold, MD (presented at the International Neuro-Ophthalmology Society Meeting, 2002), failure (progressive visual loss postoperatively or need for reoperation) occurred in 42 cases (13%). The most commonly reported complications are extraocular motility dysfunction (often transient) and pupillary abnormalities. Extraocular movement dysfunction, usually caused by lateral rectus palsy, generally resolves. Visually threatening complications are rare. Transient and protracted postoperative blindness have been reported (59,60) and are attributed to ischemic injury to the optic nerve. The complication risks after reoperation are approximately the same as those for the first procedure (61,62).

<table>
<thead>
<tr>
<th>TABLE 5. Complications of optic nerve sheath decompression</th>
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<tbody>
<tr>
<td>Extraocular movement dysfunction</td>
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<td>Pupillary dysfunction</td>
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<tr>
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<td>Choroidal ischemia/infarction</td>
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<td>New visual field defect</td>
</tr>
<tr>
<td>Orbital hemorrhage</td>
</tr>
<tr>
<td>Transient or protracted blindness</td>
</tr>
<tr>
<td>Globe perforation</td>
</tr>
</tbody>
</table>
TABLE 6. Complications of lumboperitoneal shunting

- Shunt valve or tubing obstruction
- Over-shunting (low pressure headache)
- Catheter migration/abdominal pain
- Lumbar radiculopathy
- Infection
- CSF leak
- Cerebellar tonsillar herniation (acquired Chiari malformation)
- Shunt dependency

CSF Diversion Procedures

A CSF diversion procedure treats IIH by lowering ICP but requires insertion of a foreign body. Lumboperitoneal (LP) shunting because insertion and maintenance of patency may be more difficult in the latter procedure. However, VP and cisterna magna shunting may be successfully used (63,64,67). Complications of shunts are summarized in Table 6. The revision rate for lumboperitoneal shunts ranges from 38% to 64%, with an overall revision rate of 52% (78 of 150 cases) (46,61-66). The number of revisions per patient is 2.3% to 6.6% (mean 3.9%), but this value may be skewed because of the small number of reported patients. The reported interval between shunt placement to first revision is 9 to 27 months (46,66,67). Major causes of shunt failure include catheter obstruction, low ICP, catheter migration, and lumbar radiculopathy (66,68). A programmable shunt valve usually prevents low-pressure headaches, obviating the need for reoperation; this complication is less frequent in VP than in lumboperitoneal shunting. Visual loss may herald shunt malfunction, but may also occur with a functioning shunt (66-75). Uncommonly, patients may become “shunt dependent” after being in remission for years, with worsening of signs and symptoms when the shunt is obstructed or removed. Severe, acute ICP elevation upon insertion or removal of a shunt has been reported (70). Over-shunting may lead to an acquired Chiari malformation or chronic intracranial hypotension. The symptoms and signs of low ICP are often similar to those of elevated ICP. Most patients will experience a postural headache that worsens with sitting or standing. Neck pain, vomiting, photosensitivity, blurred vision, transient visual obscurations, peripheral visual field loss, and sixth nerve paresis may occur (71). MRI changes of intracranial hypotension include leptomeningeal enhancement, tonsillar herniation, and subdural effusions (72,73).

Bariatric Surgery

Bariatric surgery may be considered in morbidly obese patients in whom medical and surgical treatments are ineffective (31). Although the procedure has risk, it offers the additional health benefits of reduced cardiovascular risk, type II diabetes, and lumbar disc degeneration that occur with significant weight loss. Bariatric surgery may be considered for long-term management but is not an appropriate treatment of patients with actively worsening vision.

SPECIAL CONSIDERATIONS

“Malignant” IIH

Aggressive treatment is required for patients in whom rapid visual decline (“malignant” IIH) develops. Significant visual field loss and marked papilledema are evident at presentation, often with decreased visual acuity. Visual loss may occur rapidly over days to weeks. Temporizing management includes serial lumbar punctures or insertion of a lumbar drain, and the administration of intravenous acetazolamide and corticosteroids (76). Prompt surgical treatment is indicated with ONSD, shunting, or both procedures. Cerebral venous sinus thrombosis is an important diagnostic exclusion as it is managed with heparinization and, in some cases, thrombolytic treatment. Occasionally, the thrombosis may not be apparent on the initial MRI study, and re-imaging or catheter angiography may be fruitful.

IIH in Pregnancy

Although pregnancy is not considered an independent risk factor for IIH, the disease may start or worsen during pregnancy (21,77). IIH during pregnancy is managed in cooperation with the obstetrician. Often the condition is successfully controlled with headache management and serial LPs. Patients are advised to avoid excessive weight gain with guidance from their obstetrician. Low-calorie diets and weight reduction are not recommended. Acetazolamide is a category C medication in pregnancy (risk cannot be ruled out because data are lacking). However, large clinical experience among neuro-ophthalmologists indicates overall safety without known teratogenic effects on the fetus, especially if the medication is used after the first trimester. Another option is chlorthalidone, a diuretic with a category B rating (no evidence of risk in humans). Corticosteroids may be administered without undue risk if needed for visual loss. Surgery is rarely required. If it is, ONSD is preferred over shunting because of potential shunt obstruction by the enlarging uterus (77). No special measures are required for delivery, and vaginal delivery is not contraindicated.

IIH in Children

Treatment of children with IIH is similar to that of adults, with the caveat that a secondary cause is often found in children (78-81). IIH in children may follow a febrile
illness, and common secondary causes are tetracycline (including minocycline), hypervitaminosis A (including retinoid use), and cerebral venous sinus thrombosis (81).

REFERENCES

Idiopathic Intracranial Hypertension

Cerebrospinal Fluid Diversion Procedures

Hugh J. L. Garton, MD, MHSc

Abstract: Cerebrospinal fluid (CSF) diversion procedures remain the principal method of treatment of hydrocephalus and an important option in treating idiopathic intracranial hypertension. Recent advances in CSF shunt hardware offer some promise in reducing the rate of complications. Third ventriculostomy has become an increasingly practiced alternative to conventional shunting in an ever-widening patient population. Long-term follow-up studies have identified complications of lumboperitoneal shunt placement. Advances in surgical navigation suggest that ventriculoperitoneal shunting may be a viable alternative in patients with idiopathic intracranial hypertension. (J Neuro-Ophthalmol 2004;24: 146-155)

Diseases of disordered cerebrospinal fluid (CSF) mechanics, including hydrocephalus and idiopathic intracranial hypertension (IIH), are often treated with CSF diversion procedures, accounting for nearly 70,000 hospital admissions in the United States alone (1).

CSF FLOW DYNAMICS

Although often thought to have unidirectional bulk flow from choroid plexus through ventricles to subarachnoid space, CSF movement on magnetic resonance imaging (MRI) is oscillatory and pulsatile (2). Egnor et al (3) have suggested that these observations should lead to the concept of the CSF as a harmonic resonator, buffering the arterial pulsations and transferring them to the venous system, while shielding the capillaries from pulsatile flow. These authors suggest that communicating hydrocephalus results not from mechanical obstruction of CSF outflow, but from a loss of arachnoid buffering capacity to arterial pulsations, resulting in a relative shunting of blood flow to the choroidal vasculature. This shunting is said to lead to increased pulsations of the choroid plexus and to increased local intraventricular pressure as measured across the cortex. As a result, the ventricular system dilates, with the accumulation of CSF passively filling the newly available space.

These theories, which have been questioned (4) and remain to be validated, have not yet been extended to IIH. Nevertheless, sagittal sinus venous pressures have been shown to be increased in case series of patients with IIH even when no anatomic obstruction is identified (5). Thus, if the primary obstruction is at the level of venous outflow, the CSF would be unable to transfer arterial pulse pressure to the venous system and result in an increase in intracranial pressure (ICP). The ventricular system in this instance would not dilate because both subarachnoid and intraventricular spaces are affected equally with no preferential flow to the choroid plexus vasculature and no transmural pressure gradient. The lack of ventriculomegaly would be further explained by the decrease in the brain’s compliance to compression as the result of increased resistance to venous outflow.

Impairment in the buffering capacity of CSF is also part of the proposed pathophysiology of syringomyelia occurring in the context of the Chiari I malformation. Loss of communication between the cranial and spinal subarachnoid space leads to inappropriate elevations in pulse pressure in the spinal subarachnoid space caused by the piston effect of the cerebellar tonsils. This leads to syrinx formation, probably through a combination of CSF being forced into the spinal cord through perivascular channels in the cord itself and the forced rostral and caudal movement of fluid within the cord as a result of the spinal subarachnoid pressure waves (6).

Debate continues to surround basic concepts of CSF reabsorption. Although traditional teaching is that CSF reabsorption occurs at the arachnoid granulations, experimental animal evidence suggests that at least a portion of CSF may drain through the lymphatic system of the head and neck, particularly in the region of the cribriform plate and the olfactory bulb, as well as through the cranial and spinal dural root sleeves (7). However, the substantial variability in mammalian CSF physiology has cast doubt on the applicability of animal models to humans (8).

TREATMENT OF HYDROCEPHALUS

The CSF shunt remains the most used treatment option for hydrocephalus. It is relatively safe with a procedural mortality of 0.1% (9) and 0.13% (based on death of one of 731 patients treated in two recent randomized trials).
Cerebrospinal Fluid Diversion Procedures


However, the complication rate, in terms of shunt failure, remains high. For children undergoing first shunt insertion, one-third can expect shunt failure within the first year, and just more than half will require shunt revision within two years (10,11). Those with primary aqueductal stenosis may fare better (12).

Endoscopic Third Ventriculostomy

To avoid the problems of shunt failure, endoscopic third ventriculostomy (ETV), in which the floor of the third ventricle is surgically opened using an endoscope placed within the ventricular system through a burr hole, has become the initial treatment of choice for certain forms of obstructive hydrocephalus, such as aqueductal stenosis. It is being attempted with varying success in conditions often not thought to be based on intraventricular obstruction. These conditions include CSF shunt obstruction and infection (13,14) and hydrocephalus in which the obstruction is considered either at the outflow of the fourth ventricle or at the arachnoid spaces around the brainstem caudal to the prepontine cistern to which the third ventricle is being opened. In either of these two situations, ETV may be indicated even though all four ventricles are dilated, suggesting communicating hydrocephalus (15). Other conditions for which ETV has been performed include hydrocephalus associated with Chiari I malformation (16) and normal pressure hydrocephalus (17,18).

Success rates for ETV depend, predictably, on the mechanism of the hydrocephalus, with rates as high as 65% to 70% for patients undergoing the procedure for aqueductal stenosis (19–21), but only 23% for neonates with hydrocephalus from an intraventricular hemorrhage (22). Most failures occur soon after the procedure is performed, although there has been at least one reported failure six years after the procedure (21). The mortality rate after ETV has been estimated at 1% (23). Complications include subarachnoid hemorrhage, basilar artery injury, and hypothalamic/ pituitary injury. There is yet no solid evidence of substantial benefit over conventional shunting in the initial few years after treatment; longer follow-up studies will be necessary to prove long-term benefit (24,25).

Despite the promise of ETV, many patients are not candidates for the procedure. Strenuous efforts continue to be aimed at improving the longevity of conventional CSF shunt systems.

Endoscopic Shunt Insertion

The neuroendoscope has also been applied to CSF shunt procedures in an attempt to position the intraventricular catheter at a distance from the choroid plexus to avoid proximal catheter obstruction. Kestle et al (17) tested this proposition in a controlled trial in which 395 patients were randomized to undergo their first shunt placement with or without the neuroendoscope. The neuroendoscope patients had a 42% one-year shunt failure rate as compared with 34% among controls. On follow-up computed tomography scanning, the two groups had similar rates of choroid plexus avoidance. Thus, although the premise that choroid plexus avoidance will improve shunt survival remains untested, neuroendoscopy evidently does not provide a simple avenue to achieve this goal (11).

CSF Shunt Valves

CSF shunt systems usually include a valve to regulate the drainage of CSF. Several innovative shunt valves have come into more widespread use in the past few years. Although the most common finding at surgical exploration of a failed shunt is a blocked ventricular catheter, this often appears to be the result of excess CSF drainage and collapse of part of the ventricular system around the catheter. Alternatively, overdrainage of CSF can lead to a uniformly small ventricular system and symptoms related to insufficient CSF volume. The valve in the CSF shunt system plays the critical role in regulating CSF outflow. Shunt valve design modification has thus been focused on limiting these complications.

Valve systems are grouped within four broad categories: 1) differential pressure valves (often called “standard” valves); 2) anti-siphon valves; 3) flow-regulated valves; and 4) adjustable valves.

Differential Pressure Valves

These function by requiring a pressure gradient across the valve to prompt CSF drainage. Different mechanisms have been used to achieve this. For example, in one design, CSF must push apart a thin slit in a silicone membrane to pass through the valve. In another, CSF must push up a small ruby ball against a spring to pass the valve (Fig. 1). When tested on the bench top, these mechanisms maintain a stable pressure with increasing flow rates through the valve. In the clinical situation, in which the ICP is variable, flow rates through these valves increase with increasing ICP. These valves are supplied in varying fixed opening

FIG. 1. Standard differential pressure shunt valve, ball-spring mechanism. The valve pressure is determined by resistance of the spring to deformation. Reprinted with permission.
pressures.Crudely, the higher the opening pressure of the valve, the less the drainage for a given range of ICPs.

**Antisiphon Valves**

Overdrainage of CSF is caused in part by a siphoning effect through the shunt system. When the patient is not supine, the distal portion of the ventricular CSF shunt system is almost always below the level of the ventricles. This creates the potential for a siphon effect, increasing the flow through the shunt system even at low ICPs. Antisiphon valves use a differential pressure valve system but add an additional antisiphon component. This can involve a silicone membrane that collapses into and blocks the distal tubing whenever atmospheric pressure (transmitted through the skin) is sufficiently higher than pressure in the distal tubing (Fig. 2). A second device uses a small weight and gravity to rotate the internal parts of the valve when the patient’s position changes from horizontal to vertical, directing CSF flow through different pressure components of the valve for the two positions.

**Flow-Regulated Valves**

CSF production does not vary with ICP, at least at typical ICP values. One way to reduce the overdrainage seen with differential pressure valve systems is to drain CSF at a constant flow rate regardless of pressure. This may be more analogous to normal drainage physiology, in which certain events that increase ICP (coughing, straining) also increase venous pressure, narrowing the pressure difference and reducing CSF drainage. Flow-regulated valves use this principle by allowing ventricular pressure changes to vary the size of the drainage aperture of the shunt valve inversely with respect to pressure. The larger the pressure, the smaller the aperture (Fig. 3). Balanced properly, the flow rate remains constant over the range of physiologic ICP. At very high pressures of CSF, these valves convert to differential pressure systems as a safety mechanism.

**Adjustable Valves**

One of the challenges in CSF shunting is determining which pressure will best suit a patient’s needs. For example, a relatively low pressure valve might be desirable in an infant, where normal physiologic ICP values are in the 3 to 5 mm Hg range. With the child’s growth, a higher pressure valve would be better to avoid overdrainage. Reoperation to change valve pressure carries a morbidity of shunt infection and malfunction. Adjustable shunt valves allow for differential pressure adjustments transcutaneously, usually with the use of a magnet to rotate internal components of the valve mechanism to a new position that increases or decreases resistance (Fig. 4) One potential complication of this type of shunt valve is accidental valve adjustment caused by environmental exposure to magnetic fields. Retrospective evidence suggests that this phenomenon, although rare (26), may occur even with household magnets in the range of 0.1 tesla if the magnet is placed within 1 cm of the valve (27).

Despite solid theory and bench-top data, there is still no class I evidence that these new valves accomplish their stated purpose. Drake et al (10) were the first to compare the different categories of CSF shunt valves in a randomized fashion. Their study found no differences in shunt survival between patients treated with a standard differential pressure valve, an antisiphon-equipped valve, or a flow-regulated shunt valve. The study enrolled patients undergoing first shunt placement, and therefore involved a high percentage of young children. Even at four years after shunt insertion, there was no difference in outcomes between the
three types of valves (28). In a large prospective study of children and adults with hydrocephalus treated with the OSV II flow-regulated valve (29), the shunt failure rate at two years was only 33%, considerably lower than the rate typically seen in patients with standard differential pressure valves. However, this study (29) lacked a control group and used different outcome measures than have been used in the more robust clinical trials.

Among the many commercially available adjustable valves (made by Strata, Sophy, and Codman-Medos), only the Codman-Medos valve has been subjected to a randomized comparison to other valve types (12). In that randomized study of 235 patients undergoing first implant and 142 patients undergoing revisions, the adjustable valve and control group experiences were similar over the two-year study period. Valve removals occurred in 32% versus 39%, and overall shunt survival rates were near 50% for initial shunts and 43% for revision shunts, regardless of treatment arm. The overall infection rate was 9.8%. Other outcomes that were similar between the treatment groups were patient sense of wellness and persistent ventriculomegaly (24% with adjustable valves, 18% with standard valves) (12). Case series reports in children have also yet to demonstrate an advantage of the adjustable devices over older, less expensive designs (30).

Given these negative randomized trials, what principles can be applied to the selection of the CSF shunt valve for a given patient? If one is using a differential pressure system, the highest pressure valve that still improves the patient’s condition is generally the most desirable. Many of the long-term complications of CSF shunt placement appear to relate to overdrainage of CSF, including restricted head growth with cranio-cerebral disproportion, slit ventricle syndrome, and overdrainage headache. Knowledge of the patient’s typical ICPs may help in judging how much pressure will be tolerated. Patients with traumatic brain injury and subarachnoid hemorrhage may require relatively less resistance to achieve adequate drainage. Patients with venous outflow obstruction in achondroplasia, and those with IIIH might benefit from high-pressure valves to retain sufficient intracranial CSF for compensation to changing intracranial volume conditions and to limit collapse of the ventricular system around the shunt catheter. Flow-regulated valves may be appropriate in any of these conditions and generally will drain less CSF than medium to low pressure differential pressure systems. Antisiphon systems are also routinely used by some practitioners; they are appropriate when the siphoning pressure will be high (tall adults) or when the distal pressure will be low (ventriculopleural shunts, because the pleural space has subatmospheric pressure during inspiration). The ability of adjustable valves to modify CSF outflow has advantages in certain other situations. For example, very young children undergoing shunt insertion are at higher risk for shunt infection than are older patients (29,31). One potential reason for this is that children with very thin skin are more likely to leak CSF out around a shunt system that puts up resistance to CSF drainage. To avoid this early after surgery, heavy drainage promoted by a low-pressure valve setting can keep ICP very low, whereas more standard drainage patterns can be achieved by raising the shunt valve pressure once incisions have healed (32,33). If no other factors are considered, differential pressure valves are clearly the least expensive, being nearly 10 times lower in cost than the current generation of adjustable valves.

**Antibiotic-Impregnated Catheters**

Antibiotic-impregnated catheters have recently been used to reduce the rate of infection that occurs in 7% to 12%
TABLE 1. Outcomes after optic nerve sheath fenestration

<table>
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<th>Pts</th>
<th>Eyes</th>
<th>Mean follow-up (mo)</th>
<th>Visual acuity improved post-op (%) (by # of eyes)</th>
<th>Visual acuity improved or stable post-op (%) (by # of patients)</th>
<th>Visual acuity improved post-op (%) (by # of eyes)</th>
<th>Visual acuity improved or stable post-op (%) (by # of patients)</th>
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</tr>
</tbody>
</table>

of shunt operations (34,35). Perioperative antibiotics reduce the rate of infection only when the native infection rate is at the upper limit of the usual range (>15%) (35). Randomized testing of the use of antibiotic-impregnated catheters for CSF shunts has not yet been reported. However, a recent trial of their use in external ventricular drainage demonstrated a significant (18% vs 37%) reduction in bacterial catheter colonization and in positive CSF culture rates (1.3% vs 9.4%) (36). Controlled studies are underway.

TREATMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION

Intracranial Pressure Monitoring

The diagnosis and treatment of IIH generally requires that the ICP as measured by lumbar puncture be more than 25 cm H2O. There are patients whose symptoms and signs are suggestive of elevated ICP but whose lumbar CSF pressures are within the normal range, borderline, or variable, or in whom lumbar CSF pressure measurement is technically difficult. In other cases, the clinical manifestations are equivocal, yet lumbarperitoneal (LP) opening pressures are elevated. In these situations, direct ICP monitoring may be considered. The procedure allows continuous telemetry and may identify periodic elevations in pressure not identified on a one-time assessment. Using a burr-hole monitor that did not require cannulation of the ventricle, Gucer et al (37) demonstrated pressures ranging from 100 to 500 mm H2O in IIH patients. Although clearly more invasive than the lumbar puncture, the risk of clinically significant hemorrhage with current similar techniques has been reported to be in the range of 0.38% to 0.7% (38), offering a favorable risk–benefit ratio in challenging cases.

Surgery

Although medical therapies are generally successful, surgical therapies are indicated for patients with symptoms.

TABLE 2. Outcomes after CSF shunt

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Eyes</th>
<th>Mean follow-up (mo)</th>
<th>Visual acuity improved post-op (%) (by # of eyes)</th>
<th>Visual acuity improved or stable post-op (%) (by # of patients)</th>
<th>Visual acuity improved post-op (%) (by # of eyes)</th>
<th>Visual acuity improved or stable post-op (%) (by # of patients)</th>
<th>Visual fields improved post-op (%) (by # of patients)</th>
<th>Visual fields improved or stable post-op (%) (by # of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornblath, 1989 (41)</td>
<td>18</td>
<td>36</td>
<td>36</td>
<td>1/5 (20.0%)</td>
<td>NR</td>
<td>27/27 (100.0%)</td>
<td>2/24 (8.3%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rosenberg, 1993 (43)</td>
<td>37</td>
<td>74</td>
<td>31</td>
<td>28/68 (41.2%)</td>
<td>29/37 (78.4%)</td>
<td>60/74 (81.1%)</td>
<td>b</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Eggenberger, 1996 (44)</td>
<td>27</td>
<td>54</td>
<td>77</td>
<td>16/28 (57.1%)</td>
<td>14/14 (100.0%)</td>
<td>28/28 (100.0%)</td>
<td>b</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Burgett, 1997 (46)</td>
<td>30</td>
<td>60</td>
<td>35</td>
<td>10/14 (71.4%)</td>
<td>16/17 (94.1%)</td>
<td>33/34 (97.1%)</td>
<td>18/25 (64.3%)</td>
<td>17/17 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Tulipan, 1998 (45)</td>
<td>7</td>
<td>14</td>
<td>9</td>
<td>8/12 (66.7%)</td>
<td>7/7 (100.0%)</td>
<td>12/12 (100.0%)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
refractory to medical management. This occurs in an estimated 18% to 22% of IIH patients (39–41). Surgical options include optic nerve sheath fenestration (ONSF) and CSF shunt. A recent Cochrane systematic review identified no randomized controlled trials comparing these treatments to each other or to medical management (42).

The CSF shunt appears to come closer to correcting the root cause of the problem, whereas ONSF focuses on protecting the vulnerable optic nerve head. Clinical outcome data comparing CSF shunt and ONSF are limited to competing case series (Tables 1–3). Comparisons are difficult because the outcome measures are often generalized to “visual symptoms” in case series of treatment with CSF shunts, while being quite specific about visual function measures in ONSF case series. ONSF series typically report results in terms of the number of eyes treated, whereas shunt series report number of patients treated. Better outcomes tend to be reported after both types of surgeries in which follow-up is short. ONSF and shunt procedures have changed over time and complication rates in early series may not reflect current results.

Shunt treatment appears to be successful in halting deterioration or improving visual manifestations in 78% to 100% of patients (Table 2) (40, 43–45). This is at least com-

### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Visual field improved or stable post-op (*) (by # of eyes)</th>
<th>Delayed visual deterioration (*) (by # of patients)</th>
<th>Delayed visual deterioration (*) (by # of eyes)</th>
<th>Shunt rate (%)</th>
<th>Improved headache</th>
<th>Optic nerve injury (*) (by # of eyes)</th>
<th>Diplopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>31/38 (81.6%)</td>
<td>1/28 (3.6%)</td>
<td>1/40 (2.5%)</td>
<td>3.6%</td>
<td>11/17 (64.7%)</td>
<td>7.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>29/29 (100%)</td>
<td>2/29 (6.9%)</td>
<td>NR</td>
<td>0%</td>
<td>9/19 (47.4%)</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>10/10 (100%)</td>
<td>2/6 (33.3%)</td>
<td>2/10 (20%)</td>
<td>NR</td>
<td>9/19 (47.4%)</td>
<td>0.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>13/14 (92.9%)</td>
<td>0/10 (0%)</td>
<td>0/14 (0%)</td>
<td>NR</td>
<td>NR</td>
<td>0.0%</td>
<td>NR</td>
</tr>
<tr>
<td>20/21 (95.2%)</td>
<td>NR</td>
<td>0/14 (0%)</td>
<td>NR</td>
<td>NR</td>
<td>0.0%</td>
<td>NR</td>
</tr>
<tr>
<td>68/75 (90.7%)</td>
<td>20/54 (37%)</td>
<td>24/75 (32.0%)</td>
<td>7.4%</td>
<td>NR</td>
<td>0.0%</td>
<td>NR</td>
</tr>
<tr>
<td>13/15 (86.7%)</td>
<td>3/11 (27.3%)</td>
<td>3/15 (20%)</td>
<td>36.4%</td>
<td>NR</td>
<td>0.0%</td>
<td>NR</td>
</tr>
<tr>
<td>20/23 (87%)</td>
<td>2/14 (14.3%)</td>
<td>2/23 (13%)</td>
<td>14.2%</td>
<td>6/19 (36.4%)</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>23/25 (82.1%)</td>
<td>2/39 (22.3%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.0%</td>
<td>NR</td>
</tr>
<tr>
<td>71/81 (87.7%)</td>
<td>11/81 (13.6%)</td>
<td>16/158 (10.1%)</td>
<td>16.3%</td>
<td>8/81 (13.1%)</td>
<td>0.6%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

Pts, patients; NR, not reported; post-op, postoperative; #, number.

* Data are presented both by eyes and by patients to allow for comparison with CSF shunt outcome data.
† Denominator refers to patients with abnormal visual acuity/visual field before ONSF; numerator refers to patients who improved postoperatively.
‡ For patients undergoing multiple ONSF, final outcome is used regardless of the number of procedures performed.
§ Delayed deterioration includes all patients deteriorating after apparent period of stability, including those who subsequently improved with additional procedures.
†‡ Shunt rate = % of patients undergoing CSF shunt placement after ONSF.

### TABLE 2. Continued

<table>
<thead>
<tr>
<th>Visual fields improved or stable post-op (*) (by # of eyes)</th>
<th>Delayed visual deterioration (*) (by # of patients)</th>
<th>Delayed visual deterioration (*) (by # of eyes)</th>
<th>Improved headache</th>
<th>Optic nerve injury (%)</th>
<th>By person abducens palsy resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>36/36 (100.0%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>b</td>
<td>1/37 (29.7%)</td>
<td>20/74 (27.0%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>b</td>
<td>NR</td>
<td>NR</td>
<td>18/18 (100.0%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>34/34 (100.0%)</td>
<td>NR</td>
<td>NR</td>
<td>3/4 (75.0%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NR</td>
<td>0/14 (0.0%)</td>
<td>0/14 (0.0%)</td>
<td>0/14 (0.0%)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Pts, patients; b, reported as “visual change,” designating a combination of visual acuity and visual field outcomes; NR, not reported.
TABLE 3. CSF shunt-related complications

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Eyes</th>
<th>Mean follow-up (mo)</th>
<th>Shunt procedures performed</th>
<th>Average survival of first shunt (mo)</th>
<th>Mean # operations (including placement)</th>
<th>Patients requiring at least one reoperation</th>
<th>Revisions per shunt-year exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comblath, 1989 (41)</td>
<td>18</td>
<td>36</td>
<td>36</td>
<td>Lumbar: 34</td>
<td>NR</td>
<td>1.9</td>
<td>38.9%</td>
<td>0.30</td>
</tr>
</tbody>
</table>
| Rosenberg, 1993 (43) | 37  | 74   | 31                  | Lumbar: 73
Ventricular: 10 | Unclear                          | 2.2                                      | 51.4%                                     | 0.48                              |
| Eggenberger, 1996 (44) | 27  | 54   | 77                  | Lumbar: 93
Ventricular: 0 | 11                                    | 3.4                                      | 55.6%                                     | 0.38                              |
| Burgett, 1997 (40) | 30  | 60   | 35                  | Lumbar: 156
Ventricular: 0 | 18                                    | 5.2                                      | 60.0%                                     | 1.44                              |
| Tulipan, 1998 (45) | 7   | 14   | 9                   | Lumbar: 0
Ventricular: 7 | NR                                  | 1.0                                      | 0.0%                                     | 0                                 |

parable with the case series success rates of 73% to 100% for ONSF (Table 1) (46-53). Failure rates up to 30% have been reported for shunt (40,43,44) and ONSF treatment (46-51,53,54). Control of headache appears to be slightly better with shunt treatment, although Kelman et al (52) reported a 90% rate of improvement with ONSF (Table 1).

The clear disadvantage of CSF shunt treatment is the incidence of shunt failure. Case series of patients managed with LP shunt placement report reoperation rates of 44% to 63% over variable time periods (Table 3) (40,43,44). However, on closer review, several patterns with respect to shunt revisions in these patients are apparent. First, relatively few patients are responsible for the majority of revisions. For example, in the series of Burgett et al (40), two (7%) of 30 patients accounted for more than 50% of revisions. Thus, the average number of procedures is poorly reflective of the typical experience. Still, more than half the patients appear to require at least one reoperation. Another confounding factor is that the indications for shunt revision are variable. Persistent or recurrent headache has often been an indication for shunt revision. Many clinicians would reserve surgical revision for patients with evidence of intracranial hypertension and visual deterioration. In case series, persistent headache appears to account for up to 21% of "shunt failure" and for 1.6% to 28% of revisions (43). Overdrainage may explain some of these headaches. Newer valve technology may reduce the need to reoperate for overdrainage. Whether patients with prominent headaches and IIH are better candidates for shunt insertion than ONSF, as suggested by Banta (51), remains unproven.

Whereas ONSF avoids long-term implant placement and its attendant problems, ONSF has its own acute complications. Optic nerve injury, retinal artery occlusion, and diplopia appear to be the main reported surgical complications, occurring at rates of 1% to 10% and 3% to 5%, respectively (Table 1). However, more recent ONSF case series generally report lower rates of complications, suggesting that procedure modifications or a learning curve are at play.

Lumboperitoneal Shunts

The LP route has traditionally been the method of shunting in IIH. This technique has been preferred because of the perceived difficulty in cannulating a normal or small lateral ventricle and to avoid the small risk of hemorrhage while passing a catheter through the brain parenchyma. As with other aspects of the treatment of IIH, reliable comparative data are unavailable. Acknowledging this limitation, the failure rate of LP shunts appears to be higher than that of ventriculoperitoneal (VP) shunts in the typical adult population. The CSF pressure transmitted to the LP shunt valve is quite different than that transmitted to a VP shunt valve. CSF pressures measured at a lumbar-positioned valve are much higher in the sitting than supine position (average, 490 mm Hg sitting, 140 mm Hg supine) (55). Siphoning is not an issue in LP shunts. Shunt valves designed to handle these pressures typically require two separate differential pressure mechanisms, one for the sitting or standing position, the other for the supine position, with a gravity-operated ball valve mechanism directing flow to the appropriate portion of the system. In addition to the usual mechanisms of shunt occlusion, these systems can be prone to stick in either the vertical or the horizontal position.

Perhaps because of overdrainage common with all shunt systems, LP shunts can be responsible for an iatrogenic Chiari I malformation. In reviewing the pediatric experience with LP shunts (for varied indications that included IIH), Chumas (56,57) noted a 70% incidence of tonsillar herniation through the foramen magnum with criteria compatible with a diagnosis of acquired Chian I malforma-
TABLE 3. Continued

<table>
<thead>
<tr>
<th>Shunt revisions for headaches alone</th>
<th>Vision deteriorates despite working shunt</th>
<th>Revisions induced by low pressure headaches</th>
<th>Revisions not related to visual symptoms</th>
<th>Patients accounting for 50% of symptoms</th>
<th>Tonsilar herniation</th>
<th>Symptomatic tonsilar herniation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>NR</td>
<td>25.0%</td>
<td>100%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>No</td>
<td>19.8%</td>
<td>16.9%</td>
<td>30.1%</td>
<td>27.0%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yes</td>
<td>0.0%</td>
<td>15.2%</td>
<td>Unclear</td>
<td>11.1%</td>
<td>7.4%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Yes</td>
<td>0.6%</td>
<td>1.6%</td>
<td>100%</td>
<td>6.7%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NR</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Pts, patients; NR, not reported.

tion. Six (4%) of 143 patients in that series became symptomatic and one died of hindbrain herniation. However, Rekate (58) found no case of acquired Chiari I malformation in a 25-patient pediatric LP shunt case series. This complication has also been reported in adults (59–61). Johnston et al (61) detail the incidence of acquired Chiari I malformation in a large population of patients with medically and surgically treated IIH. Two (4.5%) of 44 patients treated medically were found to have asymptomatic Chiari I malformation whereas 11 (14%) of 77 patients treated surgically were found to have Chiari I malformation, three (4%) of whom were symptomatic. MRI detection of the malformation occurred at three to four years after shunt placement. In patients with acquired Chiari malformation, a variety of treatment options are available, but conversion to a ventricular or cisternal shunt is a reasonable first step (61). The true likelihood of this complication in the IIH population remains unclear without well-designed prospective studies, but vigilance for the symptoms of foramen magnum compression and associated syringomyelia are warranted, particularly in children in whom the incidence of an acquired Chiari malformation may be higher (56, 62).

Ventriculoperitoneal Shunts

VP shunts are a viable alternative to LP shunts in treatment of IIH. Operatively, VP shunt placement is easier than LP shunt placement, which requires a lateral position, particularly in obese patients. Cannulation of even a small frontal horn can generally be performed using standard external landmarks or with simple assist devices (63). If head shape or ventricular anatomy suggest that standard maneuvers for ventricular cannulation may be insufficient, advances in stereotactic surgical navigation have made it feasible to cannulate very small ventricular systems reliably. In a small case series with short follow-up, Tulipan (45) reported stereotactic VP shunt placement in seven patients with IIH. All had improvement in optic disc swelling, and six had improvement in headache without need for reoperation. VP shunts avoid the risk of inducing a Chiari I malformation, and may be less likely to overdrain. A wider range of shunt valve options is available for VP than for LP shunts, with the caveat noted about the lack of proof as to the benefits of these valves. As indicated, IIH patients may be best served by a relatively higher pressure shunt system, possibly with an antisiphon system to limit overdrainage. Adjustable shunts are particularly attractive when headaches are a prominent symptom because a range of pressures can be tested for results without reoperation. These technical factors likely add up to fewer complications with the VP than LP shunt systems.

Shunt Failure

Regardless of the shunt system used, patients with IIH are no less prone to shunt failure than those with other diagnoses. Shunt obstruction caused by mechanical occlusion of the catheter or valve, or to disconnection of the shunt system, is usually met by a return of the presenting symptoms, with progressive headaches and loss of vision being the two main clinical features reported. Unfortunately, neither of these two manifestations is very specific to shunt failure, and objective measures of shunt function are needed to confirm malfunction. Because patients with IIH typically show no change in ventricular size when ICP increases, brain imaging is not useful in suspected shunt malfunction. A plain x-ray of the shunt can show a disconnection but does little to rule out the possibility of catheter obstruction. ICP measurements are thus often indicated, by shunt tap,
lumbar puncture, or, in certain circumstances, ICP monitoring. Shunt infection is usually suspected on the basis of symptoms of shunt obstruction with the addition of fever, meningismus, and abdominal pain (or other symptoms specific to the terminal site of the shunt system). Infection is most likely to occur within three months of a previous shunt operation, becoming relatively rare beyond 12 months after the procedure. A shunt tap or lumbar puncture can confirm the diagnosis.

Overdrainage is another important complication of CSF shunts. Headache is the most common symptom. Classically, there is a strong positional component to the headache, akin to that seen after a lumbar puncture. Certain imaging findings, such as subdural hematoma and Chiari malformation (in the case of an LP shunt), lead quickly to the diagnosis. In a patient with an LP shunt and a horizontal-vertical valve, it is sometimes possible to identify that the valve is stuck in the wrong position. Frequently, however, imaging studies are unrevealing. In this circumstance, ICP monitoring may be of value because it allows a correlation between intermittent symptoms and ICP and allows continuous measurement in different positions. Management options usually revolve around revising the CSF shunt valve to a higher resistance system.

REFERENCES


Cerebral Venous Thrombosis

Isabelle Crassard, MD and Marie-Germaine Bousser, MD

Abstract: Cerebral venous thrombosis is an infrequent condition characterized by extreme variability in its clinical presentation and mode of onset. The combination of magnetic resonance imaging and magnetic resonance angiography is currently the best method for diagnosis. The proportion of cases of unknown etiology remains high. The prognosis, although better than previously thought, remains unpredictable. Treatment, which should be started as soon as the diagnosis is established, consists of reversing the underlying cause when known, control of seizures and intracranial hypertension, and the use of antithrombotics. Heparin should be the first-line antithrombotic agent. Recent studies have confirmed its safety even in patients with hemorrhagic parenchymal lesions. Local thrombolysis is indicated in the very rare cases that deteriorate despite adequate anticoagulation. Cerebrospinal fluid diversion or optic nerve fenestration is used for vision-threatening papilledema when intracranial pressure control is difficult.

Cerebral venous thrombosis (CVT), first described by Ribes (1) in 1825, was long thought to be a rare and severe disease responsible for alternating or bilateral focal deficits, seizures, and coma often leading to death. Diagnosis occurred only at autopsy. During the last 30 years, the rapid development of neuroimaging has contributed to a better understanding of CVT and to the recognition of its wide clinical spectrum. Heparin is the treatment of choice. The prognosis is usually good, but adverse outcomes occur unpredictably, justifying early diagnosis and rapid management.

INCIDENCE

The incidence of CVT is unknown but is certainly higher than thought on the basis of old autopsy series (2–5). This supposition is supported by the recent publication of several large clinical series (6–13). All age groups can be affected. There is, however, a small preponderance in young women because of pregnancy, the puerperium, and the use of oral contraceptives.

PATHOLOGY

As in other venous territories, a red thrombus is progressively replaced by fibrous tissue, sometimes showing recanalization. The effect of the thrombosis on cerebral tissue depends on the availability of collateral venous channels and on the propagation of the thrombus. The outcome can vary from no cerebral lesion, to edema of various degrees, to massive—often bilateral—hemorrhagic lesions called “venous infarcts.”

Cerebral infarcts are characterized macroscopically by pallor and edema of the cortex and of the adjacent white matter in the territory drained by a thrombosed vein. In addition, there are multiple petechial hemorrhages that may become confluent, especially in the white matter (2,14,15). These venous infarcts differ significantly from arterial infarcts in having more edema and less necrosis, explaining a much higher potential for recovery.

DIAGNOSIS

In contrast with arterial stroke, CVT can present with an extreme variety of symptoms, modes of onset, and clinical courses (14). This variability of clinical features depends on several factors, such as the site and extent of the thrombosis, the rate of propagation of the occlusion, the age of the patient, and the nature of the underlying disease. Thrombosis most often affects the superior sagittal sinus (SSS), the lateral (transverse) sinus (LS) (one or both) and cavernous sinus (one or both). Thrombosis of the galenic system is less frequent. Thrombosis of petrosal sinuses or isolated cortical or cerebellar veins is rare but may be underdiagnosed because of the difficulty of recognizing its manifestations. Cavernous sinus thrombosis is a complication of infections of the face, nose, or orbits.

Mode of Onset

CVT is acute (duration of fewer than two days) in 30%, subacute (duration of two days to one month) in 50% of cases, and chronic in 20% (duration of greater than
one month). Occasionally, symptoms can progress over more than six months (6). Acute onset, often associated with focal signs, is typical of obstetrical and infectious CVT. Subacute or chronic onset is frequently observed in inflammatory diseases and in coagulation disorders (8,9). The chronic pattern of onset is typical of isolated intracranial hypertension (ICH).

**Manifestations**

CVT is characterized by a wide variety of symptoms (Table 1). Headache is the most frequent, occurring in over 80% of patients (14,16). It is also the most common inaugural symptom, present in 70% to 75% of patients before the onset of other neurologic manifestations. The headache of CVT has no specific features; it can be of any grade of severity, diffuse or localized, mostly persistent but also intermittent, sometimes occurring in attacks mimicking migraine. Its duration is usually a few days, but it may arise suddenly and be severe, mimicking subarachnoid hemorrhage. Headache can occur in the absence of any other neurologic signs, raising great diagnostic difficulties.

Papilledema is present in approximately 50% of patients with CVT. It can be associated with bilateral transient visual obscurations. In the absence of treatment, papilledema can lead to optic atrophy.

Seizures occur during the course of CVT in about 40% of patients (14); they may be partial or generalized. Focal sensory or motor signs occur in 30% to 80% of patients (14); alternation from one side of the body to the other is a highly suggestive but late pattern of presentation of SSS thrombosis.

Other manifestations include aphasia, hemianopia, various cognitive disturbances, psychiatric disturbances, cranial nerve palsies, and cerebellar signs. Unilateral or bilateral sixth nerve palsy is frequent and secondary to intracranial hypertension. Some cranial nerve palsies are suggestive of a particular location: total ophthalmoplegia for cavernous sinus thrombosis; ninth and tenth nerve palsies for internal jugular vein thrombosis (17). Impaired mental status is present during the evolution of CVT in almost 50% of cases. It is, however, rarely an initial symptom (4% in Cantu series) (11). Usually moderate in degree, it is secondary to raised intracranial pressure, and associated with headache and seizures. Severely altered mental status can be a post-ictal event or a sign of deep venous system thrombosis (14).

**Patterns of Presentation**

Despite the diverse clinical manifestations and modes of onset, there are four main clinical patterns of CVT (8,14):

1. **Focal deficits or partial seizures.** If found in association with headaches, seizures, or altered consciousness, extremity weakness or sensory loss should immediately arouse suspicion for CVT. However, CVT may also manifest isolated seizures or isolated transient focal deficits, mimicking migrainous auras (18) or transient ischemic attacks. Acute persistent focal patterns of presentation mimic arterial strokes, while subacute manifestations mimic abscesses or tumors.

2. **Isolated intracranial hypertension** with headache, nausea, vomiting, papilledema, transient visual obscurations, and eventually sixth nerve palsy (8,9,14,19–21). CVT presenting as isolated ICH can be mistaken for idiopathic ICH if appropriate investigations are not performed.

3. **Subacute diffuse encephalopathy,** characterized by a decreased level of consciousness and sometimes seizures without clearly localizing signs or recognizable features of ICH. Such cases can mimic encephalitis or metabolic disorders (8,9,14).

4. **Painful ophthalmoplegia** caused by lesions of the third, fourth or sixth cranial nerves, chemosis and proptosis (2,22–23) in patients with cavernous sinus thrombosis. In some cases, often because of the masking effect of an

**TABLE 1. Principal clinical manifestations in reported series of cerebral venous thrombosis**

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Einhaupl et al (13)</th>
<th>Cantu and Barrinagarrementeria (11)</th>
<th>Authors’ series*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 71)</td>
<td>Puerperal CVT (n = 67)</td>
<td>Nonpuerperal CVT (n = 46)</td>
</tr>
<tr>
<td>Headache</td>
<td>91%</td>
<td>88%</td>
<td>70%</td>
</tr>
<tr>
<td>Papilledema</td>
<td>27%</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>66%</td>
<td>79%</td>
<td>76%</td>
</tr>
<tr>
<td>Seizures</td>
<td>48%</td>
<td>60%</td>
<td>63%</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>56%</td>
<td>63%</td>
<td>59%</td>
</tr>
</tbody>
</table>

* Adapted with permission (14).

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inadequate antibiotic regimen, cavernous sinus thrombosis can take a more indolent form with an isolated sixth nerve palsy, mild chemosis, and proptosis (22). Extension to other sinuses and stenosis of the intracavernous portion of the internal carotid arteries are particularly dreaded (22).

Many other unusual manifestations have been reported, including subarachnoid hemorrhage simulating a ruptured intracranial aneurysm (16,24), recurrent transient neurologic deficits (8,9,25), migraine-like phenomena (18), hearing loss (17,26), isolated amnesia (27), confusion, and isolated psychiatric disturbances. These symptoms can be inaugural and are particularly misleading in the puerperium, when they are often mistaken for postpartum psychosis (14,28). Finally, CVT can also be asymptomatic, particularly in the case of LS thrombosis, which can be found on a routine computed tomography (CT) scan (29).

Investigative Studies

Computed Tomography

CT of the brain, usually the first investigation performed on an emergency basis, is useful to rule out many of the conditions that can be mimicked by CVT. It can also show abnormalities suggestive of CVT (8-12,14,29), such as the dense triangle (occlusion of SSS by fresh clot on noncontrast CT), the empty delta sign (filling of collateral veins in the SSS wall after contrast injection, contrasting with the absence of enhancement of the clot inside the thrombosed sinus), the cord sign (visualization of a thrombosed cortical vein on non contrast CT), and a LS hyperdensity (visualization of the thrombosed LS). Contrast CT scan can be useful in demonstrating cavernous sinus thrombosis as multiple irregular filling defects with bulging cavernous sinuses and enlarged orbital veins.

Noncontrast CT can also detect such nonspecific changes as brain swelling, and localized hypodense or hyperdense areas corresponding to “venous infarcts.” Nonhemorrhagic infarcts are almost as frequent as hemorrhagic infarcts, which are often multifocal or petechial. In SSS thrombosis, they are seen superficially in the cerebral hemispheres. In deep venous system thrombosis, they are seen within the basal ganglia. Contrast CT may also reveal gyral or ring enhancement in areas of venous infarctions and territorial enhancement. However, in up to 30% of cases, the CT is normal, particularly in patients with isolated intracranial hypertension. Other neuroradiologic investigations, such as magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), helical CT venography or conventional angiography, are frequently necessary to demonstrate abnormalities (8,9). They can confirm the diagnosis by showing the thrombosis and by precisely delineating its location.

![FIG. 1. Unenhanced axial CT shows left cerebral hemispheric hemorrhagic venous infarct caused by lateral (transverse) venous sinus thrombosis.](image)

Magnetic Resonance Imaging and Magnetic Resonance Angiography

MRI, in combination with MRA, is currently the modality of choice for the diagnosis and follow-up of CVT (8,9,14,30–32) (Figs. 2 and 3). The advantage of MRI is direct visualization of the clot in the sinus (Fig. 2). It can also show the associated cerebral lesions. The clot can have different appearances based on the duration of the thrombosis. At a very early stage (<five days), the occluded vessels appear isointense on T1 MRI and hypointense on T2 MRI. This is the only time when MRI gives a false negative result. It can be corrected with MRA, which shows the missing sinus. A few days later, the flow void is absent and the thrombus becomes hyperintense, first on T1 and later on T2 MRI. This change corresponds to the conversion in the thrombus of oxyhemoglobin to methemoglobin. It occurs on or about day five after the onset of symptoms and lasts until day 30 to 35. After the first month, MRI patterns are variable because the thrombosed sinus can either remain totally or partially occluded or can recanalize and return to normal. In the majority of cases, there is an isointensity on T1 and hyperintensity on T2 MRI. At six months, abnormalities persist in about two-thirds of cases. The signal is then often heterogeneous but predominantly isointense on T1 MRI and isointense or hyperintense on T2 MRI.
Cerebral Venous Thrombosis

Figure 2. T2 coronal MRI shows increased signal in superior sagittal sinus (thin arrow) with left cerebral hemispheric infarct (thick arrow).

The interpretation of MRI is usually straightforward, particularly when the thrombosed sinus is hyperintense both on T1 and T2 images and on different slices. However, in some cases, false-negative and false-positive images occur. False-negatives are rare and represent acute thrombosis studied during the very early stage, thrombosis of isolated cortical veins, and partial recanalization of the sinus. In these cases, MRA is indispensable in showing the absence of flow in the affected sinus (Fig. 3). False positives occur when there is a slow flow of blood without thrombosis. To differentiate flow artifacts from a thrombus, time-of-flight techniques are useful.

MRI is also useful in showing the parenchymal lesions secondary to venous occlusion, including brain swelling with normal signal, edema or infarction with hypointense, or isointense signal on T1 MRI and hyperintense signal on T2 MRI, or hemorrhagic infarct with hyperintense signal on both sequences (33). Diffusion-weighted imaging (DWI) (34–38) shows a pattern highly different from that of arterial infarcts, usually a heterogeneous signal intensity with normal or increased apparent diffusion coefficient (ADC), signifying vasogenic edema combined with some areas of cytotoxic edema. Another pattern consists of multifocal increased signal with moderately decreased ADC; this signal pattern predicts a low likelihood infarction compared with that which follows arterial occlusion. In a third pattern, there is no abnormality on DWI. Thus, the DWI/ADC pattern of brain lesions in CVT is highly heterogeneous, mostly suggestive of vasogenic edema and markedly different from that of arterial infarcts. This difference probably corresponds in part to the much better recovery observed in venous occlusion than in arterial occlusion.

Helical Computed Tomography Venography

Helical CT venography has recently been developed as an excellent tool to detect CVT (39). Frequent abnormalities obtained in the case of CVT are filling defects, sinus wall enhancement, abnormal collateral venous drainage, and tentorial enhancement. CT venograms may be easier to interpret and have fewer artifacts than MRA. They may be especially helpful in the very acute or late stages of CVT, when MRI can be misleading.

Conventional (Catheter) Arteriography

Conventional arteriography has been the key procedure in diagnosis of CVT for many years and is still necessary in cases of diagnostic difficulty such as cortical vein thrombosis (14,25,30,40). It requires four-vessel injection.

Figure 3. 2D Time-of-Flight coronal magnetic resonance angiogram (MRA) shows absence of signal in right lateral (transverse) and sigmoid venous sinuses suggesting thrombosis.
with visualization of the entire venous phase. The most reliable sign of CVT is the partial or complete lack of filling of veins or sinuses (Fig. 4). Some indirect signs include dilated collateral veins with a corkscrew appearance, delayed venous emptying, and dilated collateral circulation. Some locations can be difficult to interpret such as the anterior third of the SSS and the left I.S, which may be hypoplastic.

**Lumbar Puncture**

Lumbar puncture remains useful to measure intracranial pressure and as a means to decrease it if it is elevated and threatening vision. The cerebrospinal fluid (CSF) formula is often abnormal, with an elevated protein level (50%), excessive red blood cells (60%), or leukocytosis (30%) (14). CSF analysis may also be crucial to rule out meningitis.

**CAUSES OF CVT**

CVT can occur in a great variety of causes and underlying conditions. (Table 2) (14).

**Septic Cerebral Venous Thrombosis**

The incidence of septic CVT has been considerably reduced in developed countries since the introduction of antibiotics with only 10% of CVT currently attributed to infection (22,41). Septic CVT is usually caused by a contiguous propagation from infection of the ethmoid, sphenoid, or mastoid sinuses, or to hematogenous spread from the nose, ear, face, or neck. Purulent meningitis can also be a cause or consequence of CVT. A more distant focus is exceptional (41).

**Puerperal Cerebral Venous Thrombosis**

In young women, CVT occurs more frequently during the puerperium than in pregnancy and remains very common in developing countries.

**Oral Contraceptive-associated Cerebral Venous Thrombosis**

Oral contraceptive (OC) use is an important cause among women with CVT in developed countries. OC can

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**TABLE 2. Recognized noninfectious settings for cerebral venous thrombosis**

<table>
<thead>
<tr>
<th>Focal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head or neck tumors compressing cerebral venous drainage pathway (cholesteatoma, meningioma, metastasis, jugular tumors)</td>
</tr>
<tr>
<td>Occlusion of the internal jugular vein</td>
</tr>
<tr>
<td>After head injury</td>
</tr>
<tr>
<td>After neurosurgery</td>
</tr>
<tr>
<td>After lumbar puncture, epidural, or spinal anesthesia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic</th>
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</thead>
<tbody>
<tr>
<td>General surgery</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Puerperium</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Severe dehydration</td>
</tr>
<tr>
<td>Systemic malignancy (especially visceral carcinoma, lymphoma, leukemia)</td>
</tr>
<tr>
<td>Inherited thrombophilia (especially antithrombin III, protein C, or protein S deficiency, factor V Leiden and prothrombin gene mutations, hyperhomocysteinemia, antiphospholipid antibodies, disorders of fibrinolysis, sickle cell disease, paroxysmal nocturnal hemoglobinuria)</td>
</tr>
<tr>
<td>Acquired prothrombotic state (disseminated intravascular coagulation, thrombotic thrombocytopenia, heparin-induced purpura, cryofibrinogenemia, hyperviscosity, myeloproliferative disorders)</td>
</tr>
<tr>
<td>Polycythemia (ven and secondary)</td>
</tr>
<tr>
<td>Thrombocytopenia (primary or secondary)</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Hepatic cirrhosis, Crohn disease, ulcerative colitis</td>
</tr>
<tr>
<td>Vasculitis (systemic lupus erythematosus, Behçet disease, Wegener granulomatosis, giant cell arteritis)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Medications (especially corticosteroids, L-asparaginase, epsilon-aminocaproic acid)</td>
</tr>
</tbody>
</table>

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**FIG. 4.** Conventional (catheter) arteriogram shows no dye in a superior sagittal venous sinus suggesting thrombosis.
also be associated with congenital thrombophilia, reinforcing the need for an extensive coagulation work-up.

Hypercoagulability-associated Cerebral Venous Thrombosis

Among the numerous noninfective medical conditions related to CVT, congenital thrombophilia is the most frequent, particularly the increased resistance to activated protein C with factor V Leiden mutation and the 20210 G to A mutation of the prothrombin gene. It is preferable to perform the coagulation work-up before starting anticoagulation because heparin and warfarin preclude the diagnosis of antithrombin, protein S and C deficiencies or the lupus anticoagulant. There is frequently an association among several thrombophilic abnormalities, which stresses the importance of a complete coagulation work-up even in the presence of another obvious cause or risk factor.

Idiopathic Cerebral Venous Thrombosis

Despite the continuing description of new causes, the proportion of cases of unknown etiology remains between 20% and 35% in recent series. In these cases, a long follow-up is warranted since it can lead to the identification of an underlying cause, most often a systemic disease (6).

OUTCOME AND PROGNOSIS

Before the introduction of angiography, CVT was mainly diagnosed at autopsy and thought to be lethal. In recent series, the rate of mortality appears to be lower—between 6% and 33% (6,8,9,14,42). The main causes of death are the brain lesion itself (especially in massive brain hemorrhagic infarct), uncontrolled seizures, sepsis, pulmonary embolism, underlying infection, or malignancy. Factors associated with a bad prognosis include the extreme age of the patient, a rapid onset, the presence of focal symptoms, altered consciousness, and hemorrhagic infarct (4). Thrombosis in the deep cerebral and cerebellar venous system carries a much higher morbidity than thrombosis in a dural sinus or cortical vein (14).

Among the underlying conditions, the prognosis of septic CVT is worse than that of nonseptic CVT. In one series (41), the mortality was almost 80% in patients with septic thrombosis of the SSS. In another series (43), mortality was 30% in septic cavernous sinus thrombosis. In yet another series (22), mortality was 50% if the cortical veins were affected. By contrast, postpartum CVT usually has a good prognosis, with a survival of 90% in most recent series (14).

It has long been recognized that if survival occurs in CVT, the prognosis for recovery of function is much better than in arterial thrombosis. In recent series (8–12,14), patients with CVT have recovered completely in 52% to 76% of cases. However, the prognosis remains largely unpredictable. Indeed, some cases have a catastrophic course leading to death in a few days. By contrast, there are benign (probably under-recognized) forms limited to headache, transient neurologic deficits, or epilepsy. Unlike arterial stroke, few patients are left with disabling consequences. Affecting about 15% of patients (8–12,14), these consequences consist of focal weakness or sensory loss, neuropsychologic disturbances, and visual loss. In patients with papilledema, visual loss may be insidious and should be systematically monitored with regular neuro-ophthalmologic evaluations.

The long-term outcome of CVT is not well known. Residual epilepsy has been reported usually during the first year in 10% to 30% of the patients who had seizures during the acute phase. Some reports have suggested that LS thrombosis can induce arteriovenous malformations (14). Recurrence of CVT was estimated at 11.7% in a recent series of 77 patients followed for a mean of 77.8 months (44).

TREATMENT

Treatment of CVT, which remains controversial because the natural history of this condition is so variable, is aimed at the underlying cause, its manifestations (seizures, elevated intracranial pressure, and headaches), and at containing or dissolving the thrombus.

Treatment of the Underlying Cause

This is particularly indicated in the case of septic CVT, which requires prompt and specific antibiotic therapy. In some cases, surgical treatment of the primary site of infection must be considered. Treatment of underlying malignancies or connective tissue disease should also be initiated.

Treatment of Manifestations

Anticonvulsants are required in patients with seizures but need not be prescribed prophylactically (8). The appropriate duration of treatment is unsettled.

To relieve elevated intracranial pressure, heparin is often sufficient to improve venous outflow. In patients with isolated ICH, if papilledema threatens vision, we favor lumbar puncture to remove CSF before starting heparin. This is often followed by a rapid improvement in headache and improvement of the patient’s visual function. In more severe ICH, intracranial pressure-lowering agents such as acetazolamide, glycerol, or mannitol may be used. The use of corticosteroids is controversial because of the potential inhibition of the fibrinolysis.

If vision continues to worsen, lumbar puncture may be repeated. Eventually, lumboperitoneal or ventriculoperitoneal shunt or optic nerve sheath fenestration may be performed. In the rare cases of worsening of consciousness with raised intracranial pressure resistant to all previous
treatments, ventriculostomy, lumbar CSF drainage, lateral venous bypass, and even craniectomy decompression have been used.

**Treatment of Thrombosis**

Heparin is the first-line agent. Its goal is to limit the spread of thrombus and thus to diminish the intracapillary pressure. Its use has been disputed because of the fear of an increased risk of intracerebral hemorrhage. However, there is now good evidence that heparin is safe in CVT, even in patients with hemorrhagic infarcts (14,45-47). Two randomized trials (46,47) have assessed the benefits and risks of heparin. The first trial (46) compared dose-adjusted intravenous heparin with placebo and was stopped after the inclusion of 22 patients because of a significant difference between the two groups. Eight heparin-treated patients fully recovered whereas only one placebo-treated patient did. No deaths occurred in the heparin group, but three occurred in the placebo group. The second trial (47) compared low-molecular-weight (LMW) heparin with placebo in 60 patients. There were no significant differences in adverse outcomes, defined as death or a Barthel index score greater than 15 at 12 weeks (13% in the LMW heparin and 21% in the placebo group). New or enlarged cerebral hemorrhages did not occur even in the 15 patients with hemorrhagic infarcts on initial CT. A meta-analysis of these two studies (47) has shown that heparin treatment is associated with a 14% absolute risk reduction (ARR) in mortality and a 15% ARR in death or dependency, with relative risk reductions of 70% and 56%, respectively. Though not quite statistically significant, these results favor heparin treatment. Heparin treatment is recommended in all forms of CVT, even in cases of isolated ICH to prevent the onset of neurologic deficits because of extension of the thrombus into the cerebral veins (21). Because it is impossible to predict which patients will have such an extension, heparin is recommended in all varieties of CVT. The optimal duration of heparin is not established, but with the advent of neurologic improvement, heparin therapy is switched over to oral anticoagulation (warfarin) adjusted to maintain an international normalized ratio (INR) between two and three. As in deep vein thrombosis of the legs, the usual duration of treatment is six months in the absence of underlying conditions (Behcet disease, systemic lupus erythematosus with circulating anticoagulant, high-risk congenital thrombophilia) requiring long-term treatment.

The evidence in favor of the efficacy of endovascular thrombolysis remains inconclusive. Urokinase was first reported in treatment of CVT in 1971 (48), but to date there are no prospective, randomized, controlled trials of endovascular thrombolysis in CVT. There are some uncontrolled cases (49) and a retrospective analysis of the effects of urokinase (50) administered by the internal jugular or the femoral route to approximately 50 patients. More recently, local recombinant tissue plasminogen activator (rtPA) has been used in combination with heparin (51,52). Although both treatments carry a risk of hemorrhagic complications (bleeding at the femoral puncture site, pelvic bleeding, worsening of intracranial bleeding), local thrombolysis appears safe in the absence of a hemorrhagic brain lesion. However, there is no good reason to use local thrombolysis as long as heparin seems to be working and the patient is improving, which is the case in the vast majority of patients. Thus, on the basis of the present data, there is no evidence to recommend local thrombolysis as first-line treatment (53). Local thrombolysis may be indicated if the condition of the patient worsens despite adequate anticoagulation (biologically verified) and other causes of worsening have been ruled out. This approach applies to patients with focal neurologic symptoms and signs due to a progressing thrombus and not to patients with isolated ICH, who should be treated with CSF diversion or optic nerve sheath fenestration.

Some patients who are refractory to anticoagulant therapy have undergone mechanical endovascular thrombectomy with or without stenting (54) or have had surgical thrombectomy. Still experimental, such techniques are generally performed only in highly specialized centers and only in the very few patients who have an unusually deleterious course.

**REFERENCES**

Vasculopathies Affecting the Eye

Judith E. A. Warner, MD

Abstract: The retinal arteries and veins may be involved in isolation or as the result of a systemic vasculitis. This article emphasizes neurologic diseases in which the ocular vasculature is affected.

(J Neuro-Ophthalmol 2004;24: 164-169)

Vasculopathies that involve the eye may be the result of infectious, hereditary, inflammatory, neoplastic, hypoxic/ischemic, or idiopathic disorders. In some cases, the vasculopathies are isolated to the eye; in other cases, the involvement is system-wide (Table 1).

INFECTIOUS VASCULOPATHIES

In most infectious vasculopathies, the association between infection and vasculopathy is speculative. There are few ophthalmoscopic features of the infectious or para-infectious retinal vasculitides that enable distinction. History and laboratory testing are usually necessary to confirm a diagnosis.

Human immunodeficiency virus (HIV)-associated vasculopathy is often included among infectious vasculopathies but its vascular manifestations may not be mediated by infection. Patients are usually asymptomatic but may have color or contrast sensitivity deficits. On routine examination, they are found to have cotton-wool spots and intraretinal hemorrhages in the posterior pole, believed to be a manifestation of microvasculopathy of the retina. The cotton-wool spots differ from those seen in diabetes in being more linear, often taking on a boomerang shape (1) (Fig. 1). Lesions resolve spontaneously, usually within two months (2). Although the prevalence of HIV-associated vasculopathy increases with decreasing CD4 counts, it can be seen in patients whose counts are more than 100 cells/mm³, a level at which cytomegalovirus (CMV) retinitis is unlikely. Therefore, the practice in HIV centers is to perform repeated examination on patients who have cotton-wool spots and CD4 counts more than 100 cells/mm³ (3). If the abnormal fundus findings are a result of CMV retinitis, they will worsen within two to three weeks. If they are caused by HIV-associated vasculopathy, the original cotton-wool spots will resolve, although new spots may develop.

HIV-associated vasculopathy may be related to the propensity of the virus to infect endothelial cells. Elevated levels of endothelin-1 immunoreactivity have been found, possibly causing vasoconstrictor activity (4). One interesting study (5) correlated the presence of HIV-associated retinal vasculopathy with HMPAO-SPECT evidence of reduced cerebral perfusion. The association was not correlated with acquired immune deficiency syndrome staging. The authors speculated that this reduced perfusion might explain neuropsychologic abnormalities experienced by patients with HIV-1 disease (5). When hemorrhages are extensive, anemia should be considered an explanation for the cotton-wool spots.

HEREDITARY VASCULOPATHIES

In 1988, Grand et al (6) described a kindred of patients with variable expression of an inherited cerebroretinal vasculopathy. These patients had subtle changes of the vasculature of the posterior pole most suggestive of parafoveal telangiectasia. Vision was relatively preserved, although preretinal hemorrhages occurred late in the disease. On fluorescein angiography, the foveal avascular zone was enlarged with capillary obliteration. Pathologically, there were multiple scattered microinfarctions, but no abnormalities of the retinal capillaries were discovered. Of 18 presumably affected individuals, 10 had brain masses, eight in the frontoparietal region. The masses were typically confined to the white matter and were histologically characterized by vascular abnormalities and coagulation necrosis. The vascular abnormalities were found in the medium and small arteries, and consisted of fibrinoid necrosis of vessel walls. Perivascular adventitial fibrosis was prominent. Since 1988, several cases have been described with similar features (7,8). In most cases, a familial feature is evident.

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Retinal venous sheathing is an infrequent but well-recognized phenomenon in multiple sclerosis (MS). A careful study from Liverpool in 1996 (17) documented the course of retinal venous sheathing in 23 patients with MS followed-up over six months. Six of the patients had venous abnormalities, including diffuse or focal sheathing or focal perivenous hemorrhages. One patient had arterial sheathing. For the most part, the venous sheathing/staining was static over six months, despite ongoing disease activity on enhanced magnetic resonance imaging (MRI) scans. Two patients showed resolution of retinal angiographic fluorescein leakage over the course of the study. The relationship between retinal vascular abnormalities and the disease course of MS remains to be elucidated.

NEOPLASTIC VASCULOPATHIES

Neoplasms and their treatments are notorious for producing vasculopathies via hypercoagulable states, radiation injury, or toxic chemotherapeutic regimens. Mild microvascular occlusive changes are seen commonly in association with leukemia. Plasma cell dyscrasias such as multiple myeloma, Waldenstrom macroglobulinemia, and systemic amyloidosis are associated with a variety of ophthalmic manifestations. There is an interesting report (18) of a plasma cell dyscrasia resulting in systemic deposition of light chains in the kidney and the eye. In this case, the patient presented with constitutional symptoms, bilateral recent carpal tunnel surgery, and severe retinal nonperfusion. The patient had bilateral intraretinal hemorrhages, cotton-wool spots, and neovascularization of the discs. Fluorescein angiography showed capillary nonperfusion, but no venous stasis was reported. Specific staining for light chains revealed extensive deposition in the blood vessels of various biopsy specimens. Testing for hyperviscosity, including cryoglobulins, cryofibrinogen, quantitative immunoglobulins, and serum viscosity, was negative.

The well-described carcinoma-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) frequently show severe retinal vascular attenuation. There have been several reports of presumed paraneoplastic retinopathies with diffuse retinal vessel staining on fluorescein angiography, particularly involving veins (19,20). Although treatment with corticosteroids resulted in improvement in the vasculitic features, there was no improvement in vision. One patient had melanoma-associated retinal bipolar cell antibodies in his IgG serum fractions (19); the other patient had small cell lung cancer and serum reactivity to the 62kd (rather than the typical 23kd) band of bovine retinal homogenate (20). Retinal vasculitis is rare in the CAR/MAR syndromes, and its presence does not seem to be the major pathologic change. However, vasculitis as a neoplastic and paraneoplastic phenomenon occurs in a wide variety of cancers.
TABLE 1. Vasculopathies affecting the eye

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Retinitis pigmentosa-associated (28)</td>
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<tr>
<td>Cerebroretinal vasculopathy with brain masses (Grand syndrome) (6,7,8)</td>
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</tr>
<tr>
<td>Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) (9)</td>
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</tr>
<tr>
<td>Hereditary vascular retinopathy with migraine and Raynaud phenomenon (10)</td>
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<tr>
<td>Inherited retinal arteriolar tortuosity (29)</td>
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<td>Amyloidosis (30)</td>
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<td>Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy Cadasil (31)</td>
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<td>Inflammatory</td>
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</tr>
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<td>Sarcoidosis (33)</td>
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<td>Multiple sclerosis (17)</td>
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<td>Acute posterior multifocal placoid pigment epitheliopathy (14,15)</td>
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<td>Vasculopathy of herpes zoster ophthalmicus (48)</td>
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<td>Hypermunoglobulin D (61)</td>
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<td>Melanoma-associated retinopathy (19)</td>
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TABLE 1. Continued

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<td>Takayasu arteritis (65,66)</td>
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<td>Toxic</td>
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<td>Ergot alkaloids (67)</td>
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<td>Cranial/orbital irradiation (68,69)</td>
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<td>Idiopathic</td>
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<td>Eales disease (27)</td>
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<td>Idiopathic polypoidal choroidal vasculopathy (70)</td>
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<td>Idiopathic retinal vasculitis, aneurysms, and neuro-retinitis (71)</td>
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<td>Parafoveal telangiectasia (72)</td>
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<tr>
<td>Idiopathic recurrent branch retinal artery occlusions (26)</td>
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<td>Susac syndrome (22–25)</td>
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HYPOXIC/ISCHEMIC VASCULOPATHIES

Neovascularization is an abnormal vascular proliferation in response to hypoxia. It is a well-recognized late effect of ocular ischemic syndrome caused by carotid disease, diabetes, hypertension, or after central retinal vein occlusion. Neovascular vessels can occur in various structures of the eye, including retina, optic nerve head, and iris. Iris vasculopathy is a feature of exfoliation syndrome. In this case, the stimulus for micro-neovascularization appears to be deposition of exfoliation material in vessels progressing from the adventitia to the endothelium, resulting in obliteration of the lumen and consequent anterior chamber hypoxia (21).

IDIOPATHIC VASCULOPATHIES

Among the idiopathic vasculopathies is Susac syndrome, or retinooculoencephalocerebral microangiopathy of the brain and retina. Originally reported by Susac in 1979 (22), and later elaborated by O’Halloran (23), among others, it is a perplexing condition typically affecting young women. Patients have multiple, usually bilateral, branch retinal artery occlusions (Fig. 3), hearing loss attributed to cochlear arterial occlusion, and central nervous system abnormalities characterized as encephalopathy, memory loss, and headache. MRIs usually show lesions within the corpus callosum and cerebral gray matter. The CSF shows elevated protein and often mononuclear cells. Brain biopsies have shown microinfarcts, some with evidence of perivascular inflammatory infiltrates. Petty et al (24) found sparse peri-arteriolar inflammatory cells on muscle biopsies in three of five patients. In one specimen, swollen vascular endothelium nearly occluded some small arterioles. The disease can remain active for several months to several years, and may remit spontaneously. However, a recently re-
FIG. 2. Hereditary endotheliopathy including retinopathy, nephropathy, and stroke. Fluorescein angiogram shows parafoveal telangiectasia, microaneurysms, and capillary dropout. (Courtesy of R. W. Baloh, MD.)

reported case documented recrudescence after a hiatus of 18 years (25).

In 1986, Gass et al (26) reported a small series of patients with idiopathic recurrent branch retinal artery occlusions. There were nine patients, seven of whom were men, with recurrent arterial occlusions, no uveitis, and in whom systemic evaluation was unrevealing. There was no evidence of embolic material. Again, the features on fluorescein angiography were retinal arterial/venous staining with capillary non-perfusion. Three patients (one woman and two men) had auditory complaints (auditory hallucinations 1, tinnitus 2). Perhaps they represent a forme fruste of Susac syndrome.

Eales disease is a noninflammatory occlusive disorder of the retinal vasculature that causes recurrent hemorrhages in the retina and vitreous and ischemic changes in the eye. Most patients are men in the fourth decade of life. It may represent a tissue response to bacterial or tubercular antigens. Central nervous system manifestations were reported in six of 17 patients (27). Fluorescein angiography shows peripheral non-perfusion and retinal venous staining (Fig. 4), which appears to be a step along the path towards neovascularization, hemorrhages, and progressive visual loss.

REFERENCES


FIG. 3. Susac syndrome. Fluorescein angiogram shows multiple branch retinal artery occlusions. (Courtesy of H. O'Halloran, MD.)

FIG. 4. Eales disease. Fluorescein angiogram shows hyperfluorescence of peripheral veins. (Courtesy of Paul S. Bern­stein, MD, PhD.)


Vasculopathies Affecting the Eye

55. Saran BR, Pomilla PV. Retinal vascular nonperfusion and retinal neovascularization as a consequence of cytomegalovirus retinitis and cryptococcal choroiditis. 
This review includes highlights of some of the 72 platform presentations and 22 posters at the 41st Japanese Neuro-Ophthalmology Society meeting held in Kyoto, Japan, December 12-13, 2003. There were approximately 300 registrants, mostly full-time or part-time practitioners of neuro-ophthalmology in Japan. The meeting president was Satoshi Kashii, MD (Kyoto).

**TOXIC OPTIC NEUROPATHY**

Tomohiro Saijou et al (Tokyo) reported a case of optic neuropathy presumed to be caused by a side effect of linezolid (United States brand, Zyvox), an antibacterial agent. A 27-year-old woman had a bone marrow infection with methicillin-resistant Staphylococcus aureus during corticosteroid treatment of lupus. She was started on 1,200 mg linezolid per day, and within three months she noted blurred vision in both eyes and numbness in both legs. Her visual acuity was 20/30 OU. Visual fields showed central scotomas in both eyes and funduscopic examination showed bilateral disc edema. She was diagnosed as having optic neuropathy caused by systemic lupus erythematosus and treated with 1,000 mg intravenous methylprednisolone for one day. Visual acuity worsened to 20/200 OU. The linezolid was discontinued, and in two months, visual acuity recovered to 20/20 OD and 20/25 OS. The optic discs returned to normal. This appears to be the second report of optic neuropathy associated with linezolid.

**LEBER HEREDITARY OPTIC NEUROPATHY**

Reiko Kubo et al (Tokyo) reported three cases of Leber hereditary optic neuropathy (LHON) with a point mutation at 14,484 or 9,804, and showed the clinical differences from the more common LHON with a point mutation at 11,778. The two LHON cases with a point mutation at 14,484 showed some visual improvement and the LHON case with a point mutation at 9,804 showed chronic visual deterioration.

Yuzo Nakao et al (Osaka) compared three LHON 11778 cases in which the mother was the same but the father was different. Visual acuity varied between three families from 20/200 to 20/25. Considering that LHON cases with different point mutations have a similar clinical course, we do not know why Japanese patients have such clinical variability.

**ISCHEMIC OPTIC NEUROPATHY AND PAPILLEDEMA**

It is well known that the eNOS gene plays a major role in controlling vascular contractility. In a study that compared 13 patients with nonarteritic ischemic optic neuropathy (NAION) and 101 healthy controls, Tutomu Sakai et al (Tokyo) sought to determine the relationship between NAION and the eNOS gene. Abnormal mutation in the eNOS gene was positive in 15.38% of patients with NAION but in only 1% of controls.

Tetsuo Ogino et al (Hokkaidou) reported a case of transient visual loss caused by vitreopapillary traction. A 26-year-old woman noted blurred vision OS. Her visual acuity was 20/20 OU. A relative afferent pupil defect was present OS, and a visual field showed an enlargement of the blind spot and a centrocecal scotoma OS. Funduscopic examination showed a blurred optic disc margin with preretinal and subretinal hemorrhage around the left optic disc. One month later, the relative afferent pupil defect disappeared and the visual field defect was improved without treatment.

Hideki Chuman et al (Miyazaki) reported a case of pseudotumor cerebri syndrome secondary to a dural arteriovenous fistula. A 76-year-old man noted chronic blurred vision in both eyes. His visual acuity was 20/60 OU. A Goldmann visual field test showed an enlargement of the blind spot in both eyes, and funduscopic examination showed bilateral disc edema. Brain magnetic resonance imaging (MRI) was normal. Lumbar puncture opening pressure was 300 mm H2O with no abnormality in the fluid constituents. MRI and magnetic resonance angiography (MRA) denied a dural sinus thrombosis. However, MRA showed a slight enlargement of the left occipital artery, and a catheter cerebral angiogram showed a dural fistula between the left lateral sinus and the left occipital artery. The
right sigmoid sinus was 90% occluded. The authors speculated that the fistula created high pressure in the dural venous sinuses, which could not be compensated because of poor flow in the right sigmoid sinus. The fistula was considered too complex to treat, so a stent was placed in the stenotic right sigmoid sinus. After stent placement, cerebrospinal fluid pressure decreased to 5 mm H₂O, as measured by lumbar puncture, and the papilledema improved.

**OPTIC NEURITIS**

Jonathan D. Trobe (Ann Arbor, MD) delivered an invited lecture on the current management of optic neuritis. His main points were: 1) optic neuritis is usually part of multiple sclerosis (MS); 2) a normal MRI at the time of the first attack of optic neuritis identifies a group with very low chance of MS; 3) a small minority of patients with optic neuritis, a normal MRI, and a very swollen optic disc have thus far not developed MS in 10 years of follow-up in the Optic Neuritis Treatment Trial conducted in the United States; 4) baseline MRI predicts relapses but not future disability; more sophisticated MRI sequences undergoing study may do better; 5) the best predictor of disability is the pace of the illness; 6) neurologic and visual disability after optic neuritis are relatively mild; 7) corticosteroid treatment at the time of acute optic neuritis hastens recovery slightly but has no long-term benefit, and 8) disease-modifying agents—interferon beta and copolymer—reduce the frequency of clinical relapses and the accumulation of MRI signal abnormalities but do not substantially affect neurologic disability. The upshot of these facts is that the rationale for early treatment of optic neuritis with disease-modifying agents is still not well-founded and the agents themselves are not very effective. Future studies may bring better remedies.

**FIG. 1.** Dignitaries at the 2003 Japanese Neuro-Ophthalmology Society Meeting, Kyoto, Japan. *Standing, left to right:* Akio Tabuchi, MD, Kawasaki Medical School; Haruki Abe, MD, Niigata University School of Medicine; Satoshi Kashi, MD, Osaka Eye Hospital; Kazuo Nakatsuka, MD, Oita Medical University; Masato Wakakura, MD, Inouye Eye Hospital, Tokyo; Kazutaka Kani, Shiga University of Medical Science; Jonathan Trobe, MD, Ann Arbor, MI; Avinoam Safran, MD, Geneva, Switzerland; Hideki Chuman, MD, Miyazaki Medical College; Kenji Kitahara, MD, The Jikei University School of Medicine; Motohiro Kiyosawa, MD, Tokyo Medical and Dental University Graduate School. *Sitting, left to right:* Emiko Adachi, MD, Chiba University; Satoshi Ishikawa, MD, Tokyo University and former president of the Japanese Neuro-ophthalmology Society; Hiroko Yamamoto, MD, Fujita Health University School of Medicine.
SUPRASELLAR TUMORS AND RIDDDOCH PHENOMENON

Hiroshi Shima et al (Ishikawa) reported that 83 patients with treated suprasellar tumors and Riddoch phenomenon have a better prognosis for visual field improvement than do patients without Riddoch phenomenon.

ORBITAL DISEASE

Kimiko Gotou et al (Tokyo) described the ophthalmic manifestations of Graves disease in teenagers. Among 302 patients (36 men, 266 women) between the ages of 13 and 19 years, the authors noted prominent exophthalmos relative to that found in older adults but less prominent motility disturbances and optic neuropathy.

CAVERNOUS SINUS

In a session on cavernous sinus lesions, two infectious cases led to bilateral blindness, both occurring in a setting of previous chronic corticosteroid treatment. However, a single noninfectious inflammatory case was cured with corticosteroid treatment, emphasizing the importance of distinguishing infectious from noninfectious inflammation in this region. There were three cases of sixth cranial nerve palsy associated with Horner syndrome, reminding us how specific is this combination of findings for cavernous sinus disease. One dural fistula case presented as an isolated fourth cranial nerve palsy, a reminder that cavernous fistula is a consideration in unexplained fourth cranial nerve palsy.

INFRANUCLEAR OCULAR MOTILITY DISORDERS

In a session devoted to infranuclear ocular motility cases, Taro Nakamori et al (Aichi) described the first reported case of myasthenia gravis (MG) combined with Lambert-Eaton syndrome (LES). The patient was undergoing treatment with D-penicillamine for rheumatoid arthritis. The combination of MG and LES was diagnosed by electromyography. The authors attributed this “double hit” to an immune reaction to D-penicillamine.

Shunichi Suzuki et al (Hokkaido) analyzed three cases of superior oblique myokymia using a magnetic search coil technique. They found that the fast phases corresponded to the contracting directions of the superior oblique muscle.

One sixth cranial nerve palsy case was caused by pansinusitis. Three third cranial nerve palsy cases were caused each by a schwannoma, an inflammatory cavernous sinus lesion, and migraine. In the migraine case, Takayuki Takeshita (Miyagi) showed MRI enhancement at the root of the third cranial nerve during an attack. Between attacks, there was no enhancement. These findings added further evidence that ophthalmoplegic migraine is an inflammatory cranial neuropathy.

Akiko Masuda et al (Hyogo) reported a case of multiple cranial neuropathies caused by relapsing polychondritis. A 53-year-old woman developed a sixth nerve palsy, which cleared spontaneously; then, she consecutively presented with the third cranial nerve palsy.

FIG. 2. Dignitaries at the meeting entrance (left to right): Hideki Chuman, MD; Masato Wakakura, MD, chair of the 16th International Neuro-Ophthalmology Society (INOS) meeting to be held in Tokyo, November 29 to December 6, 2006; Avinoam Safran, MD, invited speaker; Satoshi Kashii, MD, chair of the 2003 Japanese Neuro-Ophthalmology Society Meeting; Kazuo Mukuno, MD, School of Allied Health Sciences, Kitasato University, Kanagawa, and current president of the Japanese Neuro-Ophthalmology Society.
developed right twelfth, left third, and left seventh nerve palsies, all appearing separately and disappearing without treatment. All studies were negative except for a tuberculin skin test.

NUCLEAR AND SUPRANUCLEAR OCULAR MOTILITY DISORDERS

In a session devoted to nuclear and supranuclear motility disturbances, Makiko Takagi et al (Osaka) reported a case of upgaze deficit and skew deviation caused by damage at the right midbrain between the riMLF and the posterior commissure. Atsuko Nihira (Hokkaidou) reported a case that showed an upgaze deficit from a single lesion in the medulla. Youji Takahashi (Iwate) suggested a relationship between skew deviation and vertical smooth pursuit movement. Masaki Kondou et al (Kyoto) suggested that the downgaze pathway is crossed. Hanako Matsunaga (Tokyo) reported a case of acquired ocular motor apraxia caused by global hypoperfusion after surgery for aneurysm of the thoracic artery. Noriko Koga (Tokyo) reported a rare case of alternating skew deviation between upgaze and downgaze in a patient with spinocerebellar degeneration. No family history was present and genetic examination was negative. Ken Jokura et al (Kanagawa) reported that 27 (59%) of 46 patients who entered coma after cardiac arrest had vertical eye deviation. More than 40% of patients with upgaze deviation died; all patients with downgaze deviation developed a persistent vegetative state.

VISUAL FUNCTION

Takashi Kurachi et al (Aichi) found that on-center bipolar cells and off-center bipolar cells affect the optokinetic nystagmus. Hiromasa Tsuda et al (Tokyo) reported a homonymous hemianopia caused by infarction at the lateral geniculate body. Chiharu Tanaka et al (Hokkaidou) reported a case of cerebral achromatopsia, pure alexia, prosopagnosia, and visual object agnosia caused by infarction of both occipital lobes. Masaki Yoshida et al (Tokyo) showed how diffusion tensor imaging could visualize anterograde degeneration of nerve fibers after a cerebral hemorrhage. Kunihiko Akiyama et al (Tokyo) compared the reproducibility of functional MRI from units of different institutes. They found better intra-individual than inter-individual reproducibility.

VISUAL PERCEPTION

Avinoam B. Safran (Geneva, Switzerland) delivered an invited lecture entitled "Unperceivable Borders Between Illusion and Reality in Visual Function." He pointed out that we depend on illusions as a normal aspect of life. Because environmental information is often suboptimal, perception must rely on the brain reconstruction of contours or other image features without retinal input. Although illusions generally are beneficial, in some instances they generate misleading percepts because individuals are not aware of their occurrence. Perceptual filling-in is a type of visual illusion with major clinical implications. As a result of filling-in, defects in the visual system may remain unrecognized. This leads to underdiagnosis of visual field defects and delayed treatment.

FUNCTIONAL MRI AND VISUAL EVOKED POTENTIALS

Takekazu Ohi et al (Miyazaki) reported a case of mainly upper limb visual ataxia caused by cerebral

![FIG.3. Traditional Japanese dinner at the home of Satoshi Kashii, MD. Left to right: Hideki Chuman, Avinoam Safran, Satoshi Kashii, Joan Loewenstein (Ann Arbor, MI, wife of Jonathan Trobe), and Jonathan Trobe.](image-url)
Infarction. Brain MRI showed bilateral parietal lobe infarction. Using functional MRI, Mari Sakai et al (Shiga) investigated the differential effect of viewing a solid stereogram and a random-dot stereogram. They showed that viewing the solid stereogram activated anterolateral right upper parietal lobe, whereas viewing the random stereogram activated posteromedial right upper parietal lobe.

Keiko Momose et al (Tokyo) showed the usefulness of the visual evoked potential (VEP) color contrast response for the objective measurement of contrast sensitivity in congenital vision disturbances. Using multifocal VEP, Yoshida Shimada et al (Aichi) showed that the visual signal that originates in nasal retina reaches the corresponding visual cortex 5.3 to 6.3 milliseconds earlier than the signal that originates in temporal retina.

**POSTER SESSION**

Yuri Ishida et al (Shimane) reported a case of right hemispatial neglect and right homonymous hemianopia caused by infarction of the left thalamus and left lateral geniculate body. With functional MRI, Kunihiro Asakawa (Tokyo) reported that processing of color with contour occurred in the ventral part of occipital lobe, whereas processing of color without contour occurred in the dorsal part of occipital lobe.

Hisako Hayashi et al (Kyoto) reported a case of dorsal midbrain syndrome caused by neurosarcoidosis. The patient was a 30-year-old man with light–near dissociation and skew deviation. MRI showed an enhancing area in the dorsal midbrain. Sarcoidosis was diagnosed by skin biopsy. The manifestations resolved completely after corticosteroid therapy.

**WORKSHOP**


The major mistakes made by authors are: 1) the article's title does not convey the main idea; 2) the abstract does not faithfully recapitulate the article and contains unwarranted conclusions; 3) the introduction devotes too much to describing the condition and too little to describing why the project was performed (the rationale); 4) the methods section fails to include complete data on when, where, and how the experiment was conducted and how subjects were accrued; 5) the results are poorly displayed with inadequate attention to tables, figures, and legends; 6) the discussion repeats the introduction instead of summarizing results and explaining their importance (how they confirm or depart from available knowledge) and acknowledging the limitations of the study; and 7) the references contain too many errors.

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The 29th International Stroke Conference was held on February 5–7, 2004, in San Diego, California. There were more than 500 abstracts presented as posters or platform presentations. Abstracts are published in *Stroke* 2004; 35:235–340.

**STROKE PREVENTION**

Patients with significant symptomatic intracranial large artery stenosis are often treated with anticoagulation, based on the results of the retrospective Warfarin Aspirin Symptomatic Intracranial Disease (WASID) study reported in 1995 (1). The avidly anticipated results of the recently completed prospective WASID study were reported at the 29th International Stroke Conference. This prospective randomized multicenter study compared the effects of warfarin (with a goal international normalized ratio [INR] of 2–3) versus aspirin (1300 mg/d) on stroke prophylaxis in patients with a previous transient ischemic attack or stroke referable to a major intracranial vessel with 50% to 99% stenosis. The trial was stopped early by the data safety monitoring board after enrollment of 569 patients, because of concerns related to the elevated risk of major hemorrhage in the warfarin arm. The results demonstrated that warfarin was not superior to aspirin in any of the primary or secondary outcomes, yet the rates of major hemorrhage were increased (8% in the warfarin arm, 3% in the aspirin arm). Intracerebral hemorrhage rates were not significantly different.

Based on the results of this study, patients with symptomatic intracranial disease should be treated with antiplatelet agents rather than anticoagulation. The recently reported Warfarin Aspirin Recurrent Stroke Study (WARSS) (2) failed to show the superiority of warfarin in general stroke prophylaxis. WARSS included patients with ischemic stroke from any cause except an inferred cardioembolic source, severe carotid artery disease in the neck for which surgery was planned, or procedure-related stroke. Taken together, the results of WASID and WARSS suggest that warfarin should be used for stroke prophylaxis only when there is a cardioembolic source. Given these data, intracranial vascular imaging may not be required to decide on an appropriate stroke prophylactic agent. However, many experts suggest that blood pressure and fluid management are best guided by this type of imaging.

Currently, warfarin is typically considered the most effective treatment for prevention of emboli from atrial fibrillation, yet its use is problematic because of drug interactions and anticoagulation monitoring. The results of a study testing an alternative agent were reported at the meeting. The Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation V study (called the SPORTIF V trial), with recruitment ending in 2001, was a double-blind, multicenter (409 centers in the United States and Canada) trial comparing warfarin (with a goal INR of 2–3) to a new agent called ximelagatran, a direct thrombin inhibitor, in stroke prophylaxis among patients with atrial fibrillation. The results showed no statistically significant difference between the two agents in prevention of stroke or systemic embolization. Intracerebral hemorrhage rates were similar. Currently, the U.S. Food and Drug Administration (FDA) is reviewing this agent, which could provide an alternative method of anticoagulation using an agent without known drug or food interaction, and which does not require coagulation laboratory monitoring. The drug has been associated with a threefold elevation in alanine aminotransferase in 6% of patients; this side effect seems to disappear despite continuation of the medication. The significance of this enzyme elevation remains unknown. Nonetheless, ximelagatran may represent a convenient alternative to warfarin in anticoagulation for atrial fibrillation.

Amlodipine and lisinopril were compared with chlorthalidone in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) in 33,357 patients aged 55 years or older with hypertension and one other cardiovascular risk factor (3). Previously, reports had demonstrated no difference in primary cardiovascular end points among the three treatments. Secondary end points such as heart failure were lower in the thiazide group. Stroke-related outcomes were analyzed separately and reported at the meeting. Stroke occurrence, a previously specified secondary outcome, was similar in the amlodipine and chlorthalidone arms but was lower in the chlorthalidone arm than in the lisinopril arm, attributable to a difference in subgroup analysis found only in African American/Afro-Caribbean patients. Although in this subgroup the thiazide was more effective in lowering blood pressure than was the angiotensin-converting enzyme (ACE) inhibitor, the effect
on stroke prophylaxis was not solely due to superior blood pressure control, suggesting that in these racial groups, thiazide diuretics should be considered first-line antihypertensives. The ALLHAT results differed from results of previous studies, which had shown superiority of ACE inhibitors in stroke prophylaxis, perhaps because of the difference in racial composition of the study population. ALLHAT heightens awareness that there may be significant racial differences in treatment effects of antihypertensive agents.

ACUTE ISCHEMIC STROKE

Intravenous recombinant tissue-type plasminogen activator (rt-PA) is the only FDA-approved therapy for acute stroke. Although there is a 30% improvement in excellent three-month outcome with its use, ways to improve arterial recanalization and resulting neurologic improvement are being pursued. Transcranial Doppler (TCD) is sometimes used to monitor recanalization in patients receiving thrombolysis for large artery thrombosis. This diagnostic test may actually promote clot lysis initiated by systemically administered rt-PA, a hypothesis generated by the observation that patients being monitored with TCD seemed to have better outcomes than those not monitored. The use of ultrasound-aided thrombolysis was tested in the Combined Lysis of Thrombus in Brain Ischemia With Transcranial Ultrasound and Systemic TPA trial (called CLOTBUST), a multicenter Phase II study randomly assigning patients to receive standard rt-PA treatment with infrequent TCD monitoring or to receive rt-PA with two hours of continuous TCD using a 2-MHz probe targeting the area of residual flow. The initial results of this study were reported. Symptomatic intracerebral hemorrhage risk was similar in both groups, suggesting that the addition of continuous TCD is safe. The primary outcome measure (significant early clinical improvement or complete recanalization) was achieved in 30% of the group receiving rt-PA alone and in 40% of the group receiving rt-PA plus TCD. Three-month outcomes were not significantly different between the two groups. The results of this study suggest that further clinical trials of ultrasound-assisted thrombolysis are warranted in a larger group of patients with acute stroke. If future results show efficacy, ultrasound-assisted thrombolysis may become a treatment option for middle cerebral artery thromboses.

There are no good data supporting the use of mechanical devices during endovascular treatment of acute stroke. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial tested a thrombus retrieval device in cerebral revascularization. The initial results were reported. In this trial, a balloon-guided catheter was placed proximal to the clot, blocking forward flow. The intravascular thrombus was retrieved with a corkscrew-like device. In all, 141 patients were treated. The results of the first 114 patients were reported. Revascularization was achieved in 54%. Serious device-related complications occurred in 3.5%, including vessel perforation or dissection. Device fracture was also a problem in almost 3%. Although much more information is needed regarding the safety and efficacy of this particular device, mechanical endovascular techniques hold promise in acute stroke therapy for large vessel occlusions.

Concerns continue to exist regarding the use of thrombolytics for mild stroke. An analysis using the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study database was undertaken to assess the benefits of rt-PA administered within 3 hours of a minor stroke. Five different definitions of minor stroke were given to capture patients with a low National Institutes of Health Stroke Scale (NIHSS) score and those who were likely to have had a lacunar infarction. Three-month outcomes suggested benefit in the use of rt-PA in this post hoc analysis, supporting the use of intravenous thrombolytics for patients with minor stroke. Patients with stroke causing functional disability should not be excluded from treatment with intravenous rt-PA because of a low NIHSS score.

INTRACEREBRAL HEMORRHAGE

The role of surgery in treatment of intracerebral hemorrhage has been a controversial topic. The International Surgical Treatment of Intracerebral Hemorrhage (ISTICH) trial compared the use of “early” surgery for intracerebral hemorrhage with initial conservative management. Patients who were thought likely to benefit from surgery were not enrolled. Patients were randomly assigned within 72 hours of the hemorrhage to receive either clot evacuation within 24 hours of randomization (“early surgery”) or initial conservative care. Patients in the latter group became eligible for surgery at the discretion of their treating neurosurgeon if their condition deteriorated. Greater than 25% of the group randomly assigned to receive initial conservative management ended up having surgery. There were no significant differences between the two groups in favorable neurologic outcome or mortality. The delay in surgical treatment in the “early” surgery group because of the wide enrollment and treatment windows, as well as exclusion of those thought likely to benefit from early surgery, may help account for the lack of benefit shown from early surgical intervention. Surgical intervention for spontaneous intracerebral hemorrhage is likely to remain controversial, despite the results of this study.

SUBARACHNOID HEMORRHAGE

Because cooling is known to be neuroprotective, its ability to reduce ischemic injury complicating surgical clipping of aneurysms was tested. The results of the Intraoperative Hypothermia for Intracranial Aneurysm Surgery study
were reported. This study was a prospective, randomized multicenter trial assessing the effect of intraoperative cooling on the three-month outcome of patients with aneurysmal subarachnoid hemorrhage undergoing surgical clipping. Based on this study, there does not appear to be a role for intraoperative cooling for aneurysm clipping.

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REFERENCES


Scope: This is a third edition of the first medical textbook composed as a problem-based, decision-tree analysis of clinical practice. Formulated by the three musketeers of neuro-ophthalmology, Drs. Burde, Savino, and Trobe, this edition emphasizes a stylized organization of signs and symptoms that allows the reader a clear view of the authors’ thought processes. One can appreciate the lines of logic that define the journey from clinical declarations of dysfunction to a specific pathophysiology that triggers such dysfunction. This new edition has been significantly rewritten, with timely references and additional Tables and Figures. Its text is a seasoned treatise on clinical neuro-ophthalmology that is evidence-based, and the product of perhaps a combined 75 years of clinical practice by its authors.

Content: The book is divided into 15 chapters, each organized around a sign, a symptom, or a clinical theme. Chapters include unexplained visual loss, optic neuropathy, chiasmal disorders, transient visual loss, ocular oscillations, anisocoria, eyelid disturbances, and neuro-ophthalmic disorders of psychogenic origin. There is ample text and illustration (both color and black and white), and decision trees within each chapter. Indeed, chapters begin with a helicopter-view decision tree that orients the reader to where the clinician begins, and ends, and how one gets from here to there. Dispersed within each section are management boxes—coherent, highlighted summaries that emphasize key points of clinical care. There are frequent and helpful tables and a healthy, although not overwhelming, bibliography for each section. The index is both complete and usefully organized.

Strengths: A strength of this third edition, equally true for earlier editions, is that the book can be read and processed on many levels. One can use the decision trees themselves to guide a clinical path that begins with signs or symptoms and ends with a narrowed differential diagnosis. Alternatively, the management boxes can be scanned and used as review. The text itself reads well and easily—it is succinct, nicely written, and compelling. Appendixes at the end of several chapters provide extended details on clinically relevant examination procedures and can be used independently. A great strength of the book is that while the classic party line of knowledge is presented for the readership, the authors go on to complement formal dogma in helping clinicians through the practicalities of taking care of patients and answering clinical questions. For example, in discussing the pharmacology of pupillary function testing, the authors admit that they are guided by associated clinical signs and symptoms in making their decisions, and not driven by results of such testing. They are comfortable allowing their clinical acumen to trump results of testing. This type of honesty places classic dogma in its proper perspective and allows one to balance the theory and practice of neuro-ophthalmology. The approach is wonderfully illustrated in the chapter on anisocoria, a chapter that most powerfully lends itself to a true decision tree. This chapter alone is worth the price of the book.

Weaknesses: Weaknesses are few and far between. One might argue that the authors need to differentiate probability from possibility more. The reader would benefit by relative prevalence data of different entities. For example, within the section of ischemic optic neuropathies, the rarity of a true posterior ischemic optic neuropathy is not emphasized, nor is the reader cautioned that PION might best be thought of as a diagnosis of exclusion and one that is best left to others to make. Also, one might question whether serologic studies for Lyme disease really should be included in the evaluation of patients who present with progressive symmetric binocular visual loss characterized by central or centrocecal scotomas. One has to wonder how many cases of Lyme disease have been uncovered in the Bronx, Ann Arbor, and inner-city Philadelphia.

Recommended Audience: One of the most compelling things about this text is there is something to be learned within it no matter what you bring to the table. That is, this book is for beginners, intermediates, and advanced clinicians. Every time I look through it, I pick up something useful and easily incorporated into my clinical world. The text is appropriate and relevant for students, residents of ophthalmology and neurology, fellows in neuro-ophthalmology, and neuro-ophthalmologists.

Critical Appraisal: This book is like a fine wine; it improves with age. It is wonderfully organized, innovative in its presentation, practical in its information, and overwhelmingly useful in its paradigms. The list of texts worth owning in neuro-ophthalmology is short; this text is at the top of that list.

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**Multiple Sclerosis: Current Status and Strategies for the Future**


**Scope:** This is a multi-authored and multidisciplinary textbook by the Committee on Multiple Sclerosis (MS), intended to review current knowledge so that future research dollars can be best directed and allocated. The effort included input from patients with MS. This approach allows for appeal to educated MS patients, neurology residents, primary care physicians, or general ophthalmologists.

**Contents:** The Committee reviews the clinical manifestations of the disease in short synopses. Drugs in current use and research strategies are discussed with detailed recommendations for future studies.

**Strengths:** Each section contains a gray shaded box with a simple, succinct summary of its contents. Various clinical symptoms and signs are reviewed with detailed medication alternatives, each with attendant side effects. The characterization and treatment of some of the symptoms (cognitive impairment, spasticity, bladder dysfunction, pain, and fatigue) are very good. The chapters discussing future strategies for understanding disease mechanisms and potential therapies are also excellent. I especially valued the neurobiology section, with its discussion of purported roles of astrocytes and oligodendrocytes, the mechanisms of recovery of demyelinated axons and neuronal plasticity, and the interplay of immunology and gene expression. The validity of magnetic resonance imaging (MRI) as a surrogate outcome measure is clearly and fairly presented.

**Weaknesses:** The review of some of the symptoms and signs is superficial. Each of the current disease-modifying therapies and clinical options could be discussed in more detail. Modification of the pseudoexacerbation response is not discussed. The discussion of potassium and sodium channels and 4-aminopyridine is hidden in an appendix undergoing ongoing clinical trials. A better index, too, might also help this opus.

**Recommended Audience:** This book has been well-designed to accomplish its task of helping to focus and direct research funding by presenting a simple overview of a very complicated field. The style of the chapters allows the text to appeal to people with varied backgrounds.

**Critical Appraisal:** Why do we need another book on MS? Because this is a burgeoning research field with very complicated and ambiguous immune process contributions, and multiple therapeutic options. It is difficult to digest the whole "MS story" with the myriad of published papers, each presenting only a piece of the puzzle. This applies to the novice with a new interest in MS and to the clinician experienced in the field. Every health care worker who encounters MS patients would benefit from reading the compelling chapter on "disease management and measurement." Guidelines for how we deliver the diagnosis are practical and reassuring.

The text reminds us that many patients do not want to know about demyelination, but rather about how to live. Although we sense this reality as physicians, we often revert to a more intellectual posture in our conversations with patients. The writing style of the book remains pleasantly clear, simple, and instructional, which is quite an accomplishment for a book with so many contributors.

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**Introduction to Functional Magnetic Resonance Imaging**


**Scope:** A textbook that examines the subject of functional MRI. It provides a guide to the principles and application of functional MRI rather than a detailed mathematical treatment of the fundamentals and underlying physics.

**Contents:** The book is organized into three parts, each of which has two sections. Part I is an introduction to functional neuroimaging in general. All the essential concepts are introduced and there is an overview of how functional MRI works and how it fits into the broader field of neuroimaging. Part IA describes energy metabolism of the brain, the nature of cerebral blood flow and oxygen metabolism, and basic nuclear medicine approaches to measuring these quantities. Part IB describes the basics of nuclear magnetic resonance, how an MR image is made, and how an MR signal can be related to functional activity.

Part II focuses on the principles of MRI. Part II A describes the nature of the nuclear magnetic resonance signal, sources of image contrast in MRI, and the sensitivity of the MR signal to local diffusion characteristics of tissue. Part II B describes how the local MR signal is imaged, including the basic Fourier transform relationship (the core of MRI), as well as the techniques for image acquisition, and noise and artifact analysis.

Part III deals with the techniques used in functional MR. Part III A covers tracer kinetic studies, bolus tracking experiments with MR contrast agents, and arterial spin labeling techniques for direct measurement of cerebral blood flow. Part III B focuses on the blood oxygen level dependent (BOLD) effects used in functional MR.
The appendix contains a thorough discussion of the physics behind nuclear magnetic resonance reflective of the author’s expertise in this field.

A CD-ROM is included with the figures used in the book.

**Strengths:** This text is well-written and readable. It balances theory with clinical application. For those readers wishing greater detail in mathematical theory, the author provides gray, highlighted areas that can be read in addition to the basic text. The CD-ROM is easily downloadable and contains images of figures used throughout the book.

**Weaknesses:** A welcome addition would have been a section dealing with future directions of research and applications of functional MRI, including BOLD effect.

**Recommended Audience:** Active neuroscience investigators using functional MRI in their research as well as new investigators or clinicians without previous knowledge of the field will find this text easily readable and thorough. It has much to offer the neuro-ophthalmology community.

**Critical Appraisal:** The author provides an excellent manual on an ever-expanding field. His expertise rings solidly throughout this work. It will no doubt be a great resource for both researcher and clinician alike.

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**Magnetic Resonance in the Diagnosis of CNS Disorders**


**Scope:** This is a multi-authored hard-cover text that surveys MRI findings in a broad range of disorders commonly seen in neurologic and neurosurgical practice. The monograph does not cover such newer techniques as FLAIR, diffusion and perfusion-weighted imaging, MR spectroscopy, or functional MRI. Orbital imaging is not included.

**Contents:** The book begins with a short chapter encompassing the basic physics of MRI, definitions of the various imaging sequences, uses of paramagnetic contrast media, and some features of normal MR anatomy. The remaining chapters are arranged logically according to disease processes, with chapters on cerebrovascular disease, trauma, intracranial infection, degenerative diseases, and tumors. Another chapter is devoted to MR angiography. An additional chapter is devoted to MRI in children.

**Strengths:** The book contains dramatic representative images illustrating common MRI findings of the more common neurologic disorders, accompanied by one or more representative images illustrating disorders in their very advanced stages.

**Weaknesses:** The illustrations are not of the highest resolution, although generally sufficient to illustrate pathology. The book omits many of the newer imaging techniques that have extended the usefulness of MRI. The chapter on pediatric disorders contains no text, with but nine illustrations and captions. The radiologic features of illustrations are not detailed, and no differential diagnosis is given. A brief discussion is included in the section on most disease entities, but the depth of clinical information is inconsistent and at times dogmatic and lacking in subtlety.

**Recommended Audience:** This text might be of value to medical students rotating through neurology, neurosurgery, or neuro-ophthalmology services. They would appreciate the radiologic images demonstrating gross pathology. Having mastered these images, they could graduate to more advanced neuroradiologic material. The book cannot be recommended for specialty trainees or practitioners in any of the neurologic disciplines.

**Critical Appraisal:** The radiologic images do not offer the breadth and depth of MRI findings for most disorders, and little attention is given to subtle and early findings in either rare or common conditions. Thorough differential diagnoses are rarely offered. The text seems destined for a secondary role in the more sophisticated medical libraries and likely will not command much loyalty or success.

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**Cerebrovascular Disease**


**Scope:** This is a multi-authored collection of conference proceedings assembled and collected for scientists and clinicians interested in stroke.

**Contents:** The text is the memorialization of the Proceedings of the 22nd Princeton Conference on Cerebrovascular Disease of March 2000, in 10 sections, 36 chapters, and 460 pages. It illustrates the immense understanding of the fine
natural balance of central nervous system function and the intertwined reactions to ischemia. The breath of material covered is impressive. We are reminded that “a strong case can be made for molecular oxygen in the air we breathe being the most dangerous toxin and carcinogen in the environment” and appraised of the dangers of peroxynitrite anions (derived from nitric oxide and superoxide anions). There is a concise review of drugs that prevent excessive activation of NMDA receptor-operated ion channels, a discussion of apoptosis and other possible programs of cell death, and explanation of the potential role of astrocytes in ischemic brain injury. The importance of the vast difference in glial cell numbers between the rodent brain, which is the most commonly used experimental model, and the human brain, is highlighted. In the rodent brain there are approximately equal numbers of glial cells and neurons, whereas in the human brain, more than 90% of all cells are glia. Despite this immense knowledge, no effective therapies are available. The book’s closing chapters ask, what have we learned? Justin A. Zivin attempts to answer and outlines the reasons why clinical trials of neuroprotective agents have yet to produce significant improvements in outcome after stroke.

Strengths: The symposium offers a comprehensive and accessible review of current theories of cellular and molecular mechanisms of damage, methods of assessment of ischemic damage by MRI, and potential therapeutic pathways in cerebral ischemia.

Weaknesses: This is not your basic primer on cerebrovascular disease. Indeed, this is not for the faint of heart. There is an overwhelming and potentially bewildering amount of information for readers without thorough background knowledge or the time to fully assimilate all the papers presented.

Recommended Audience: The clinician with a general interest in neuro-ophthalmology may enjoy browsing through the book to acquire an understanding of the complexity of the molecular and cellular processes initiated by cerebral ischemia. Anyone with a specific clinical or research interest in ameliorating the consequences of cerebrovascular disease will appreciate the availability of such a comprehensive review.

Critical Appraisal: To some this book will be full of hope, to others it will be full of despair. As noted by Kennedy R. Lees in chapter 35 (“Prospects for Improved Neuroprotection Trials in Stroke”), the experimental basis for neuroprotection is well-founded. Many drugs acting by a variety of mechanisms can be administered up to several hours after the ischemic insult and reductions in infarct volume can be demonstrated. Numerous strategies have been sufficiently convincing to encourage such clinical development; unfortunately, the range of drugs and mechanisms that have been
tested in the clinic exactly parallels the list of those that have failed. And so the paradox becomes obvious.

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The Aging Brain


Scope: This eighth volume of the Maps of the Mind series continues the presentation of mind–brain issues targeting a lay population while remaining mindful of a medical audience.

Contents: The book’s 10 chapters define aging in terms of its physical, social, and psychologic impacts. The author clearly presents research and discussions on the spectrum of life cycle changes of the human brain. This includes a spectrum from normal aging to dementia and its possible modulation. Included are general reference and a bibliography of primary sources.

Strengths: The author thoughtfully covers a surprising range of contemporary brain and mind research and concepts. The succinct style and casual presentations make it a painless perusal. An unusual feature of this book is the incorporation of social and environmental issues. Their integration reflects the author’s expertise and experience as a professor of mental health at the University of Aberdeen, Scotland.

Weaknesses: Paradoxically, the book’s strengths are also its weaknesses. References are not annotated and the tone is too colloquial, weakening its scientific rigor. Only one page, for example, targets an ophthalmologic audience and relates predominantly to visual sensory loss with age and its consequences.

Recommended Audience: The text is particularly useful for the physician interested in the effects of aging or for those not familiar with modern concepts of brain–mind issues, aging, and dementia. Much in the text will also be of interest to the lay public and to patients looking for more information about geriatric neurobiology.

Critical Appraisal: This is a succinct book incorporating a surprising breadth of contemporary neuroscience, easily digestible, with many thoughtful and innovative concepts about aging and the brain. Although it is a pleasurable read for anyone, it is unlikely to further educate those currently active in the medical specialties of brain or mind.

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HIV/AIDS and the Eye: A Global Perspective


Scope: This is one of the Academy’s ophthalmology monographs, number 15 in the series, that addresses human immunodeficiency virus (HIV) and its manifestations within the eye. It is a component of the “lifelong education for the ophthalmologist” (LEO) series designed to provide a framework to assist members and practitioners in their continuing medical education. The series includes a vast array of clinical products and programs that form the core of self-directed, individualized, continuing medical education and re-certification for the practicing clinician.

Contents: This monograph is divided into nine chapters, beginning with epidemiology, continuing through molecular mechanisms and prevention of HIV transmission, culminating in focal anatomic declaration of HIV infection. The clinical chapters include adnexal and orbital disease, anterior segment manifestations, posterior segment manifestations, neuro-ophthalmic manifestations, and manifestations in children. The closing chapter addresses ophthalmic manifestations of HIV in the developing world. The book concludes with an epilogue entitled “From Despair to Hope.” The text includes generous photographs, with some in color, clearly presented tables and figures, and an extraordinarily sophisticated and straightforward writing style.

Strengths: The monograph is assembled by two unusual and talented clinical scientists. The authors are sophisticated and multidimensional practitioners schooled in ocular manifestations of inflammatory disease. In addition, Dr. Cunningham holds a degree as master of public health, so that he is eminently qualified to speak to the larger world health care issues of endemic HIV infection. Dr. Belfort provides the perspective of one based in South America who has been President of the World Uveitis Symposium and the Pan American Congress of Ophthalmology. The strengths of this book are the photographs, the organization, the clarity of writing, the tables, and the cited bibliography.

Weaknesses: The only thing I could think of as a deficiency is the lack of an accompanying CD-ROM to allow access electronically to the wonderful figures.

Critical Appraisal: The success of this monograph is the simplicity of its presentations and the clarity of its illustrations. The text is also exemplary. If one wants a single singular summary of HIV as it affects the eye, this monograph is it.

Recommended Audience: The book is a wonderful summary, quick review, and appropriate overview for anyone interested in HIV infection and its effects within the visual system. It offers the strength of an atlas and the simplicity of outline presentation.

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The Requisites in Ophthalmology: Retina, Choroid, and Vitreous

Jose S. Pulido, MD. Mosby, St. Louis, 2002. ISBN: 0-3230-0237-4. $92.00

Scope: This book is one of the “Requisites in Ophthalmology” series edited by Jay H. Krachmer, MD, chair of the Department of Ophthalmology, University of Minnesota Medical School. The author, professor, and director of the Eye and Ear Infirmary in the Department of Ophthalmology and Visual Sciences at the University of Illinois at Chicago has written this volume to serve as an introduction for ophthalmology residents to diseases of the posterior segment.

Contents: Organization nicely follows clinical paradigms of examination of the posterior segment. Also included are discussions of relevant anatomy, an overview of surgical techniques, appropriate ancillary testing, and discussions of fluorescein angiography. The text proceeds according to specific disease types. Topics include diabetic retinopathy, arterial and venous disease, retinitis pigmentosa, age-related macular degeneration, tumors, phakomatoses, peripheral retinal disease, toxicities, infectious and inflammatory disease, and trauma.

Strengths: There are excellent photographs, many in color. The book is superbly organized, quite practical to read from cover to cover, and useful as a reference on a single subject. It covers very well the underlying anatomy, common causes, and current therapies.

Weaknesses: The text lacks timely references. By design, the book is a distillation of many sources of knowledge not always derived directly from literature. Indeed, the intent of this book is that it be read as a general learning tool rather than as a conduit to primary sources.

Recommended Audience. This fine book will provide an excellent beginning for residents in ophthalmology.

Critical Appraisal: The author brings forth his formidable skills and clinical experience. I recommend adding this text to the readings of residents and as a component of every practicing ophthalmologist’s library. Along with the
American Academy of Ophthalmology's Basic and Clinical Science series, this book will provide a solid foundation for a lifetime of study.

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Clinical Retina


Scope: A multiauthored textbook and atlas that presents a wide spectrum of information about both common and less usual retinal diseases. The book's goal is to provide medical students and ophthalmology residents with essential information about medical retina.

Contents: The text follows the traditional classification of retinal diseases. It is structured into 15 chapters and covers all aspects of retina, from anatomy and physiology to laser photocoagulation and PDT. Each chapter is structured to have text on the left, with accompanying images or illustrations on the right. Chapters are subdivided into sections: general information, symptoms, clinical features, ancillary testing, pathology/pathogenesis, treatment/prognosis, and systemic evaluation. Every chapter ends with timely references.

There are nice summaries of macular diseases, retinal vascular diseases, hereditary retinal disorders, drug toxicities, intraocular tumors, inflammatory diseases, trauma, peripheral retinal diseases, and diseases of the vitreous. There is a fine summary of the histopathology of retinal diseases that deserves particular mention. There is a chapter on clinical trials, including diabetic retinopathy, retinal vascular diseases, retinopathy of prematurity, and newer therapies for macular degeneration. The book itself is complemented by an accompanying CD-ROM, which contains all the photographs and illustrations displayed.

Strengths: The most successful features of this book are its iconography, the high quality of images, and the cogent text. An innovative layout permits quick access for consultation, and the many tables allow the reader to assemble a useful differential diagnosis. The enclosed CD-ROM is a source of delight for the expert ophthalmologist as well as a source of new knowledge for students and residents.

Weaknesses: The alphabetical order in which diseases are presented can lead to some difficulty in making appropriate clinical connections and cross-referencing information.

Recommended Audience: Although this textbook-atlas is designed especially for medical students and ophthalmology residents, specialists too may also appreciate it. The neuro-ophthalmologist will be especially interested in presentations of the white dot syndromes and acute zonal occult outer retinopathy. The 800 fine photographs and many comparative tables and the summary guidelines from more recent trials make the book a useful reference tool.

Critical Appraisal: I found this to be an engaging book that gave me the opportunity to see representations of rare diseases not commonly encountered. The contributing authors assembled by the editors are expert in retina disease.

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Pediatric Eye Disease: Color Atlas and Synopsis


Scope: This short pocket text provides a brisk visual overview of common pediatric eye disease. The focus is on appearance and pattern recognition as well as the differential diagnosis of the more common ophthalmic pathologic processes in childhood.

Contents: The book is a 247-page multi-authored text divided into five parts emphasizing those pediatric ophthalmic conditions seen at differing ages.

Section I, neonatal eye disease, includes six chapters covering ophthalmia neonatorum, TORCH syndromes, cataracts and developmental anomalies of the lens, glaucoma and developmental abnormalities of the anterior segment, congenital anomalies of the lid and orbit, and retinopathy of prematurity.

Section II, ophthalmic disease in infants, covers strabismus in infancy, systemic genetic craniofacial syndromes with ophthalmic involvement, developmental vitreoretinal disease, optic nerve anomalies, ophthalmic involvement in non-accidental trauma, and nasal lacrimal duct obstruction.

Section III moves on to ophthalmic disease in toddlers, and covers amblyopia and strabismus, ophthalmic infections and inflammation, ptosis, orbital tumors, and intraocular and surface tumors.

Section IV covers ophthalmic disease in school-aged children, including uveitis, nystagmus and anomalous head postures, vision development testing and visual screening, refractive errors and further orbital tumors in the young children.

Section V covers accidental trauma and spectacles in infants and children.

Each chapter has been designed to emphasize definition, differential diagnosis, work-up, treatment, and conclusions. Each chapter also includes up-to-date references. The most compelling contents are the pictures themselves, located at the end of each chapter.
Strengths: With the exception of dermatology and radiology, no field in medicine is as pattern recognition-oriented as ophthalmology. It is a weakness of many extensive texts in ophthalmology that illustrations are inadequate. That is not a weakness here. Most of the pictures presented make their points well, are of high quality, and are in color. The organizational system of patient age is user-friendly. The capsule vignettes on each diagnosis are good. Without question, however, the greatest strength of this atlas is the quality of its photographs. With only rare exception (the Peter's anomaly could be replaced and several of the pictures could be better cropped), the photographs are first-rate. They go a long way toward illustrating many of the important disease processes seen by the generalist as well as the pediatric ophthalmologist. This book would even be appropriate in a pediatrician's office, because it gives a rapid capsule summary as well as pictures to compare.

Weaknesses: Although the authors have gone to great lengths to maintain uniformity of chapters, there are significant variations. It may be unnecessary to have a second chapter on orbital tumors in "young children," because there is some degree of duplication with the earlier orbital tumor chapter; the two could have easily been combined. Separating non-accidental from accidental trauma seems artificial. The final chapter on spectacles in infants and children could have been included in earlier discussions of refractive errors.

Recommended Audience: This is a handy text for residents doing their pediatric ophthalmology rotation. It clearly supplements the excellent American Academy of Ophthalmology's Basic and Clinical Science Course section VI by including many more illustrations of common pediatric disease. The atlas would find a very nice home in the office of general ophthalmologists who see children and practicing pediatricians.

Critical Appraisal: Although suffering from some rough spots and variability, this text accomplishes its goal quite well. The pictures are good, the text is easy to read, and a wide spectrum of pediatric pathology is concisely presented.

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Field Guide to the Eyes
Jonathan D. Trobe, MD and Richard E. Hackel, MA, CRA.
Lippincott Williams & Wilkins: Philadelphia, USA, 2002.
ISBN0–7817–3168-2. $32.95

Scope: This slim, pocket-sized, heavy-jacketed paperback, written by an ophthalmologist and an ophthalmic photog-
LETTERS TO THE EDITOR

Increased Intracranial Pressure Associated With Ophthalmoplegia, Ataxia, and Areflexia

To the Editor:

Patients with idiopathic intracranial hypertension (IIH) typically present with normal examination findings except for papilledema and sixth nerve palsy. This report describes a patient with external ophthalmoplegia, ataxia, areflexia, and mild proximal weakness in addition to the other findings of IIH.

A 29-year-old woman was admitted with headache and visual loss three weeks after an abortion. The pregnancy was uncomplicated until the end of the fifth month, when she was admitted to a hospital with the diagnosis of abruptio placenta. She was discharged one week later without any symptoms. Two weeks later, she was referred to our institution with headache, neck pain, and blurred vision.

We found visual acuities of 20/50 OD and finger counting OS. Optic disc edema with peripapillary hemorrhages was present OU. There was a complete limitation of eye movements in all directions. No palsy was evident and the pupils were reactive. She had gait ataxia and mild proximal weakness (Medical Research Council grade 4) in the upper and lower extremities. Deep tendon reflexes were absent. The rest of the neurologic examination was normal.

Routine laboratory tests, cranial computed tomography, magnetic resonance imaging (MRI), magnetic resonance venography, and cerebral angiography were normal. Distension of the perioptic nerve sheaths was detected in the orbital MRI. Lumbar puncture (LP) revealed an opening pressure of 300 mm H2O. After drainage of 40 mL of CSF, the patient was begun on treatment with acetazolamide (initially 250 mg twice daily, increased gradually to four times daily) and methylprednisolone (1 mg/kg per day).

On the fifth day after admission, the motor examination, gait, and eye movements were completely normal. Headache was relieved. Despite the recovery of these symptoms, the opening pressure of a third LP performed on day 7 of admission was still elevated at 270 mm H2O. Because no improvement was detected in visual acuity, optic nerve fenestration was performed on the right eye. Corticosteroid treatment was discontinued and the patient was discharged on acetazolamide treatment.

Examination three months later showed a visual acuity of 20/30 OD and 20/200 OS, with bilateral optic nerve pallor more prominent OS. The rest of the neurologic examination was normal.

There are numerous reports of tinnitus, neck stiffness, paresthesias, ataxia, and third, fourth, fifth, and seventh cranial nerve palsies in IIH (1-5). Kidron et al (6) used the term “malignant pseudotumor cerebri” for their two patients having rapidly progressive visual loss, ophthalmoplegia, and areflexia. Friedman et al (7) reported nine cases of IIH with external ophthalmoplegia, including four cases from the former literature (6,8). In common with our patient, three have had a miscarriage. Ophthalmoplegia, ataxia, and areflexia improved rapidly, but significant visual loss remained in five of the patients.

The explanation for the ophthalmoplegia in these IIH cases remains unknown, but increased CSF pressure itself may cause it (7). Ataxia may be the result of a relative orthostatic hypotension (1). We have no explanation for the presence of weakness and areflexia. Fisher syndrome could have been the diagnosis in this patient, but the presence of normal CSF formula, normal electrophysiologic findings, and negative antibody results make this diagnosis highly unlikely. We acknowledge the many reports of Guillain-Barre syndrome or Fisher syndrome with papilledema and elevated CSF pressure (9,10), and that neither the CSF nor electrophysiologic findings by themselves are enough to rule out these diagnoses, but it would be unusual to have such rapid recovery.

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REFERENCES

Cat Scratch Disease in Two Brothers

To the Editor:

A nine-year-old boy noted decreased vision OD three days before examination. He had a flu-like illness two weeks earlier, which included intermittent fever and headaches. The family had recently acquired a four-month-old kitten, but no one was aware of being scratched.

Visual acuity was 20/40 OD and 20/20 OS with a small right relative afferent pupillary defect. Automated perimetry revealed an enlarged blind spot OD and was normal OS. There were cells in the vitreous, more marked in the OS. Optic disc edema was present OD and there were foci of retinochoroiditis in both eyes (Fig. 1).

The erythrocyte sedimentation rate was 41 mm/h and serum IgG for Bartonella henselae was positive, more than 1:256. He was treated with 250 mg azithromycin per day for three weeks.

His eight-year-old brother, who was not present during the initial examination and did not report visual loss, also had intermittent fever and headaches concurrent with his brother's symptoms. His serum IgM for B. henselae was 1:512 with an IgG more than 1:1024. He was asked to undergo an ophthalmic examination three weeks later.

Visual acuity was 20/20 OU, with normal pupils. Mild vitritis was noted OU. Funduscopy revealed mild opacification of the retinal nerve fiber layer OD with resolving parapapillary exudates (Fig. 2). The boy's mother and father had no history of visual loss, fevers, or headaches.

Cat scratch disease has been increasingly noted as a cause of optic disc edema, retinochoroiditis, and neuroretinitis (1,2). Coinfection of members in the same household would seem to be a likely result of exposure to an infected cat. However, concurrent ocular involvement has been rarely reported in members of the same family (3). Children and young adults appear to be at increased risk for systemic infection after exposure (4).

Although at least one comparative trial studying lymph node volume has suggested the benefit of treatment with systemic antibiotics (5), the treatment of ocular manifestations of cat scratch disease remains controversial (4). Most patients will have visual improvement with conservative management (6), but irreversible visual loss has been noted (7).

Members of the same household of a patient with cat scratch disease should be questioned for symptoms of systemic infection. In those with systemic symptoms, B. henselae titers should be obtained and ocular examination considered, even in those who are visually asymptomatic, particularly children, who may be less likely to report visual dysfunction.

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FIG. 1. Fundus photographs of the nine-year-old patient reveals optic disc swelling OD and areas of retinochoroiditis OS (arrows).

FIG. 2. Fundus photograph of the nine-year-old's visually asymptomatic eight-year-old brother, who had a history of fever, headaches, and elevated Bartonella henselae titers, reveals mild opacification of the retinal nerve fiber layer and resolving parapapillary exudate (arrows).
Contralateral Amaurosis After Retrobulbar Anesthetic Injection

To the Editor:

I (REW) recently performed cataract surgery on an 84-year-old woman who experienced transient contralateral visual loss after a retrobulbar block, presumably from ipsilateral optic nerve sheath penetration.

Preoperatively, visual acuity was best-corrected to 20/60 OD, 20/30 OS, entirely attributable to cataract. After intravenous sedation, 3.5 mL of 2% lidocaine was injected into the right retrobulbar space. Fifteen minutes later, before commencing the surgery, the patient stated that she could not see. This was interpreted as visual loss on the injected side, and the patient was reassured. On completion of the case 25 minutes later (40 min after the retrobulbar injection), it became apparent that the patient could not see in either eye.

Visual acuity was hand movements in the operated eye and no light perception in the unoperated eye. Motility was very limited in the operated eye and was normal except for a marked deficit of abduction in the unoperated eye. The pupil in the operated eye measured 6 mm in dim light and was minimally reactive to direct light; the pupil in the unoperated eye measured 7 mm and was unreactive to direct light. Indirect ophthalmoscopy of both eyes was normal.

No intervention or treatment occurred. Over the next two hours, the visual acuity in the unoperated OS gradually recovered to its 20/30 baseline and the visual acuity in the operated OD ultimately improved to 20/25.

Contralateral transient visual loss after retrobulbar anesthetic injection is a rare but well-recognized complication (1-6) (Table 1). Antoszyk and Buckley (3) reported the largest case series: three patients. In all three, there was evidence of contralateral visual loss and contralateral third nerve palsy, similar to the present case. They theorized that the anesthetic was injected into the subdural space of the optic nerve sheath and tracked along the ipsilateral optic nerve sheath to the orbital apex. As the anesthetic tracked posteriorly within the subdural space to the area of the chiasm, it interfered with conduction within the contralateral optic nerve and third cranial nerve.

Brod (4) reported a case of ipsilateral central retinal artery occlusion and contralateral transient visual loss after a retrobulbar anesthetic injection in which computed tomography performed 90 minutes after the injection demonstrated an air bubble within the ipsilateral optic nerve sheath, consistent with intra-nerve sheath injection.

The proposed mechanism of intra-optic nerve sheath injection and subsequent tracking of anesthetic into the intracranial subdural space is consistent with that observed in contrast orbitography (7-10), a technique used in the premodern imaging era to delineate orbital anatomy and tu-

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<thead>
<tr>
<th>Authors</th>
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<th>Procedure</th>
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<tr>
<td>Follette and LoCascio, 1985 (1)</td>
<td>67/M</td>
<td>Keratoplasty resuture OS</td>
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<td>Antoszyk and Buckley, 1986 (2)</td>
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<td>Lau et al, 2003 (6)</td>
<td>57/M</td>
<td>Cataract extraction OD</td>
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<td>Warwar et al, (present letter)</td>
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Table 1. Contralateral transient visual loss after retrobulbar anesthetic injection
mors. Local anesthetic and contrast material are injected into the retrobulbar space and plain film x-rays are taken. Reed (7) reported a patient with temporary vertical nystagmus and contralateral sixth cranial nerve palsy, and x-rays confirmed the presence of radiopaque material within the optic nerve sheath and the intracranial subdural space. Kaufer and Augustin (8) reported the presence of radiopaque material along the optic nerve and within the subdural space of the midbrain in a patient who remained asymptomatic during a three-hour observation period. Lombardi (9) reported contrast material in the intracranial subdural space in 3 (2%) of 150 orbitographies. All three patients experienced pain, nausea, and vomiting but no focal neurologic deficits. Although a 2% incidence of subdural penetration with retrobulbar injections in contrast orbitography may seem high relative to the number reported for retrobulbar anesthetic injections, orbitography allows visualization of the injected material; with retrobulbar anesthetic injections, nerve sheath injections and subdural penetrations may be asymptomatic and go unrecognized.

Cardiovascular instability and death after retrobulbar blocks have been attributed to "brain stem anesthesia" (11-13). In these cases, the anesthetic is thought to enter the cerebrospinal fluid through the subarachnoid space of the optic nerve sheath. Why some injections enter the subdural and others the subarachnoid space is unknown. Perhaps the depth of needle penetration, the force and volume of injection, or individual anatomic variations are explanations. We know of no reports of permanent contralateral visual loss or systemic neurologic sequelae after intra-optic nerve sheath injections of anesthetic agents. With the growing popularity of topical ocular anesthesia, complications related to retrobulbar injections will likely decrease. However, retrobulbar alcohol injections for blind, painful eyes are still used. Although we are not aware of any reports of intra-optic nerve sheath injection of alcohol, the effect on the contralateral nerve and/or the central nervous system could be devastating.

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Eye Movement Abnormalities in a Case of X-Linked Dystonia-Parkinsonism (Lubag)

To the Editor:
X-Linked dystonia-Parkinsonism is a rare movement disorder first described in 1976 on the island of Panay in the Philippines (1). Dubbed by local inhabitants as "lubag" for its characteristic twisting movements, it afflicts males in the third to fifth decades (2,3). We describe a man afflicted with lubag who displays eye movement abnormalities that have not been previously reported.

A 54-year-old man from the island of Panay, province of Capiz, the Philippines, had writing difficulties second to dystonic hand posturing. This was followed by slowly progressive speech difficulties, dystonic limb and trunk movements, cogwheel rigidity, and postural instability (4). When first examined in 1989, he had no ophthal- mic symptoms, and ophthalmologic examination then was remarkable only for horizontal saccadic pursuit movements.

Over the next seven years, he was treated with 25 mg carbidopa/250 mg levodopa three times daily, 100 mg

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amantadine twice daily, 5 mg selegiline three times daily, 4 mg trihexyphenidyl three times daily, and 5 mg bromocriptine three times daily.

Examination in 1996 disclosed worsening of his dystonia. Although he still had no ophthalmic symptoms, he now had markedly abnormal eye movements. In straight-ahead gaze, his eyes were aligned and there were no saccadic intrusions. Pursuit was saccadic, as before. Horizontal gaze amplitude was normal, but both eyes displayed marked limitation of upward and downward gaze, estimated as 30% and 40% of normal range, respectively. Both upper lids were retracted. Saccades were slow in all directions; optokinetic nystagmus in the horizontal and vertical planes was symmetrical. Vestibulo-ocular reflexes by doll’s eye maneuver were intact. The remainder of the ophthalmologic examination was normal.

Ocular disturbances have not previously been reported in lubag, although their presence parallels those found in other movement disorders such as Parkinson disease and Huntington disease (5,6). In particular, the patient’s eye movement abnormalities, with the primary exception of the absence of square wave jerks on primary gaze, bear a strong resemblance to those found in progressive supranuclear palsy (7).

Although progressive supranuclear palsy neuropathology includes brainstem involvement (7), autopsy studies in lubag patients have shown atrophy of the caudate nucleus and putamen (2,8). In one case of lubag with myoclonus (9), it was suggested that extrastriatal structures may have been affected, but no other areas have specifically been implicated in the pathogenesis of this disease. In this case, the patient’s marked supranuclear ocular disturbances appear consistent with brainstem deficits.

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REFERENCES


Laser Visual Field Testing

To the Editor:

In the recent issue of the journal, Michael Lee et al (1) reported the use of laser visual field testing for screening purposes. It is interesting to note that the authors used a red laser for their target. In the general male population, up to 8% may have red–green color blindness, and this might be a limitation of the testing in the subgroup. I wonder if any of the patients in their predominantly male Veterans Hospital cohort reported difficulty with the red laser target (2,3). I have also had anecdotal success using my laser pointer (green) for testing visual fields in patients at the bedside, and I agree with the authors that the technique is useful, particularly when a formal visual field is not available or impractical. I commend the authors for their novel application of new technology in addressing an old problem.

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REFERENCES


Reply:

We appreciate the comments of Dr. Andrew Lee. In our experience, patients who are red-color blind do not have trouble seeing a red laser pointer on a uniform testing background. We agree with Dr. Lee that a green laser pointer may also work for the purpose of screening.

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Upcoming Meetings

**June 26–June 30, 2004**  
14th Meeting of the European Neurological Society  
Barcelona, Spain  
http://www.ensinfo.com/  
Contact: gerard.said@bct.ap-hop-paris.fr

**June 29–July 2, 2004**  
16th International Perimetric Society Meeting  
Barcelona, Spain  
http://webeye.ophth.uiowa.edu/ips/Meetings/Barcelona04.htm  
Contact: ips2004@unicongress.com

**July 18–July 22, 2004**  
International Neuro-Ophthalmology Society (INOS)  
Geneva, Switzerland  
http://www.symporg.ch/Inos  
Contact: info@symporg.ch

**August 29–Sept. 3, 2004**  
XVI International Congress of Eye Research  
Sydney, NSW, Australia  
Contact: icer2004@tourhosts.com.au

**Sept 4–Sept 7, 2004**  
8th European Federation of Neurological Societies Congress  
Paris, France  
http://www.kenes.com/efns2004/  
Contact: efns04@kenes.com

**Sept 21–Sept 23, 2004**  
The 27th Annual Japanese Neuroscience Meeting  
Osaka International Convention Center (Grand CUBE Osaka),  
Japan  
http://www.congres.co.jp/icer2004/  
Contact: icer2004@kenes.com

**Sept 24–Sept 27, 2004**  
The European Association for Vision and Research (EVER)  
Vilamoura, Portugal  
Contact: ever@skynet.be

**October 03–October 06, 2004**  
129th Annual Meeting of the American Neurological Association

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**October 15–October 17, 2004**  
Joint Meeting of the Asian Neuro-Ophthalmology Society (ASNOS) and the Japanese Neuro-Ophthalmology Society (JNOS)  
Nagoya, Japan  
http://www.shinkeiganka.com/asnos.html  
Contact: 81-42-778-9417

**October 16–October 21, 2004**  
2004 Congress of Neurological Surgeons Annual Meeting  
San Francisco, CA  
Contact: info@1CNS.org

**October 23–October 26, 2004**  
Joint Meeting of the American Academy of Ophthalmology (AAO) and the European Society of Ophthalmology (SOE)  
New Orleans, LA  
http://www.aao.org/annual_meeting/  
Contact: meetings@aao.org

**October 23–October 27, 2004**  
34th Annual Meeting of the Society for Neuroscience  
San Diego, CA  
http://web.sfn.org/  
Contact: info@sfn.org

**Feb. 13–Feb. 17, 2005**  
Copper Mountain Resort  
Copper Mountain, CO  
http://www.nanosweb.org/meetings/  
Contact: (860) 586-7507

**March 9–March 13, 2005**  
American Association of Pediatric Ophthalmology & Strabismus Annual Meeting  
Orlando, FL  
http://med-aapos.bu.edu/  
Contact: TSPPlank@aol.com
March 18–March 21, 2005
XXV Pan American Congress of Ophthalmology
Santiago, Chile
http://www.paao.org/congress.htm
Contact: info@paao.org

April 9–April 16, 2005
57th Annual Meeting of the American Academy of Neurology (AAN)
Miami, FL
http://aan.aan.com/
Contact: web@aan.com

April 16–April 21, 2005
American Association of Neurological Surgeons 2005 Annual Meeting
New Orleans, LA
http://www.aans.org/annual/
Contact: 847.378.0500, info@aans.org

May 1–May 5, 2005
The Association for Research in Vision and Ophthalmology (ARVO)
Fort Lauderdale, FL
http://www.arvo.org/Meetings/meetgrid.asp
Contact: (240)-221-2900, arvo@arvo.org

May 21–May 27, 2005
43rd Annual Meeting of the American Society of Neuroradiology (ASNR)
Toronto, ON
http://www.asnr.org/
Contact: 630-574-0220

May 25–May 28, 2005
14th European Stroke Conference
Bologna, Italy
http://www.eurostroke.com/default.htm
Contact: Hennencii@eurostroke.org

June 14–June 18, 2005
Canadian Congress of Neurological Sciences Annual Meeting
Ottawa, ON
http://www.ccns.org/ccns_information/events.html
Contact: brains@ccns.org

June 23–June 25, 2005
47th Annual Scientific Meeting of the American Headache Society
Philadelphia, PA
http://www.ahsnet.org/calendar
Contact: ahshq@talley.com

June 25–June 28, 2005
8th European Congress of Neuropathology
Amsterdam, The Netherlands
http://www.euro-cns.org/congresseur.php
Contact: a.vanschendel@amc.uva.nl

Sept. 26–Sept. 29, 2005
130th Annual Meeting of the American Neurological Association
San Diego, CA
http://www.aneuroa.org/
Contact: 952-545-6284

Nov. 5–Nov. 11, 2005
XVIIIth World Congress of Neurology
Sydney, Australia
http://www.wcn2005.com
Contact: wcn2005@icmsaust.com.au

Feb. 21–Feb. 24, 2006
Joint Meeting of the International Congress of Ophthalmology, the Pan American Congress of Ophthalmology, and the Brazilian Congress of Prevention of Blindness
Sao Paulo, Brazil
http://www.ophthalmology2006.com.br/
Contact: info@ophthalmology2006.com.br