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Carotid Endarterectomy for Transient Monocular Visual Loss and Other Ocular Ischemic Conditions

Jonathan D. Trobe, MD

Evidence from randomized clinical trials (RCTs) is a rare and prized commodity in medicine. When it does come along, as in the case of carotid endarterectomy (CE) for stroke prevention, it evokes an amazing variety of responses (1-5).

The evidence may be rejected because it does not conform to preconceptions. It may be dismissed as out of date, especially when techniques have improved. The fine print or follow-up reports may be ignored and the evidence misapplied to subgroups that differ substantially from the general cohort. It may be applied to types of patients who were not even in the original cohort, and, most often, “statistically significant” benefits may be surmised as “clinically meaningful” without any consideration of cost.

In this issue of the Journal of Neuro-Ophthalmology, three articles (6-8) deal with the use of CE for transient monocular visual loss (TMVL) and other ophthalmic indications. It is astounding how differently the same evidence is interpreted and applied.

In a Viewpoint article, Wolintz (6) finds little robust evidence to support a meaningful benefit of CE in TMVL. The basis of her argument is an after-the-fact subset North American Symptomatic Carotid Endarterectomy Trial (NASCET) analysis by Benavente et al (9) who found that TMVL patients required at least three of the following features to benefit from CE: 1) male sex, 2) age of 75 years or older, 3) history of hemispheric transient ischemic attack (TIA) or stroke, 4) history of intermittent claudication, 5) ipsilateral internal carotid artery stenosis of 80%-94%, and 6) absence of collateral vessels on angiography. Only 20% of the NASCET cohort met those criteria. Yet, in another Viewpoint article, Nicolle and Hachinski (7) report that at the University of Western Ontario, the home of the authoritative NASCET study, CE is offered to patients of either sex and of any age if the ipsilateral cervical carotid stenosis is high grade (>70%) without consideration of how many of the above risk factors are present in the patients.

In a Point Counter Point debate on CE for TMVL, Caplan and Hertzer (8) both support the use of CE for TMVL, dismissing the findings of Benavente et al (9) for different reasons. Caplan argues that, as a large study, the NASCET could not consider individual patient characteristics such as the echographic features of the plaque, now believed to refine stroke risk. Hertzer rejects the subgroup analysis of TMVL in the NASCET report as being statistically flawed.

There is no doubt that RCT data support CE for stroke prevention in patients with transient hemispheric TIA and stroke (2,3). But do patients with clinical manifestations of ocular ischemia belong in that group? In its abstract summarizing a review of articles on CE and stroke prevention published between 1990 and 2002, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (10) affirms that “evidence supports carotid endarterectomy for severe (70 to 99%) symptomatic stenosis” but makes no exception for patients with TMVL or retinal stroke. Yet, deep within the text of the article, the authors acknowledge that “patients with hemispheric TIA/stroke had
greater benefit from CE than patients with retinal ischemic events” (10). This difference in benefit is based on the fact that medically managed patients with retinal ischemic events clearly have a much lower risk of major hemispheric stroke than do patients with hemispheric TIA or minor stroke (11).

What about the value of CE for other ophthalmic indications? Nicolle and Hachinski (7), Caplan (8), and Hertzer (8) consider central retinal artery occlusion (CRAO) as much of an indication for CE as TMVL. Yet CRAO need not be the result of an embolic event; it often appears pathologically as thrombosis within a retrolaminar atheroembolic plaque (12). In one study of 34 patients with CRAO, only 12% had ipsilateral carotid stenosis of 80% or more (13); in another study of 77 patients, only 20% had stenosis of 50% or more (14). Moreover, although the risk of hemispheric stroke in patients with CRAO has not been rigorously documented, it seems to be lower than in patients with recent hemispheric TIA or stroke (15).

Finally, what about CE for patients with asymptomatic Hollenhorst plaque? Nicolle and Hachinski (7) do not offer CE to such patients, but Hertzer (8) does, and Caplan (8) might. Is there a compelling reason to believe that the asymptomatic patient with high-grade carotid stenosis and a Hollenhorst plaque should be managed differently from the asymptomatic patient with high-grade carotid stenosis but no such plaque? An older study (16) pointed out that early death from myocardial infarction is the major risk in patients with retinal plaque. No study has directly addressed the value of CE in such patients. But the American Academy of Neurology report of 2005 (10) finds that for “asymptomatic patients with 60 to 99% stenosis, the benefit/risk ratio is smaller compared to symptomatic patients,” suggesting that in this group, “individual decisions must be made.” The authors cite the following sobering facts in relation to CE in asymptomatic high-grade carotid stenosis: 1) the Mayo study (17) was terminated early because of a high rate of myocardial infarction (22%) in the surgical group; 2) the Veterans Administration study (18) found no significant benefit of CE; 3) the Asymptomatic Carotid Artery Study (19) found that CE reduced the relative risk of ipsilateral hemispheric stroke by 53%, but the five-year risk was only 11% in the medically treated group. The small benefit would have disappeared if the peri-operative stroke rate had been more than 2.3%, a rate much lower than has been found in other studies (20); and 4) the Asymptomatic Carotid Surgery Trial (21) found that patients undergoing early CE had a five-year stroke risk of 6.4%, whereas patients undergoing delayed CE had a five-year stroke risk of 11.8%. But these data totaled all strokes, including those in the contralateral carotid and vertebrobasilar distributions.

This information leads to some inescapable conclusions: 1) TMVL should not be lumped with hemispheric TIA or stroke; the stroke risk without CE is relatively small, and the benefit from CE is not established; 2) CRAO should not be lumped with a hemispheric TIA or stroke; carotid stenosis is often mild, suggesting a non-embolic mechanism; and 3) asymptomatic patients with Hollenhorst plaques and high-grade carotid stenosis may have a stroke risk equal to that of patients without such plaques; if so, they should not undergo CE because the reduction in future stroke is too low, even if the peri-operative complications are minimal.

Two other facts ought to caution the use of CE in oculic ischemia. First, patients probably are at just as high a risk of myocardial infarction and cardiac death as are those with hemispheric TIA and stroke (14–16), which is a risk that cannot possibly be made better by CE. Second, the benefit of CE, even in symptomatic patients, depends on a peri-operative stroke and death rate less than 5% (2). In most hospitals, this rate is not tallied or made known to non-surgeons (22); when it is tallied, it is often more than an acceptable level (23). For all these reasons, it is time to remove ophthalmic ischemic conditions from the indications for CE.

REFERENCES


Ophthalmic Manifestations in 18 Patients with Botulism Diagnosed in Porto, Portugal Between 1998 and 2003

Susana C. Penas, MD, Olinda M. Faria, MD, Rosário Serrão, MD, João A. Capão-Filipe, MD, PhD, António Mota-Miranda, MD, PhD, and Fernando Falcão-Reis, MD, PhD

Background: Botulism is a rare but potentially lethal disease in which ophthalmic signs and symptoms are among the very earliest manifestations. The aim of this study was to investigate the epidemiological and clinical features of botulism-infected patients admitted to a general hospital in Porto, Portugal.

Methods: We performed a retrospective chart review of all botulism patients admitted to São João Hospital between January 1998 and January 2003. We excerpted data on epidemiology, ophthalmic and non-ophthalmic manifestations, and treatment.

Results: We identified 18 patients in nine registered outbreaks. In two patients (11%), ophthalmic manifestations preceded systemic manifestations; in six patients (33%), ophthalmic and systemic manifestations occurred simultaneously; in ten patients (56%), systemic manifestations occurred first. Ophthalmologists had examined only seven patients and made the correct diagnosis in five. The most common ocular symptoms were blurred near vision (100%), blurred distant vision (94%), and diplopia (44%). Accommodation impairment was documented in all seven patients examined by ophthalmologists.

Conclusions: Ophthalmic manifestations were among the earliest and most prominent manifestations of botulism in this series, as in earlier reports. The diagnosis should be suspected when impaired accommodation and gastrointestinal symptoms occur together.


Botulism is a disorder caused by neurotoxins produced by Clostridia species, which are strictly anaerobic gram-positive bacilli. The most common offender is Clostridium botulinum. This microorganism can present itself in two different forms: 1) vegetative, responsible for the production of toxin types A through G, and 2) spore-forming. Clostridial spores have worldwide distribution in soil, fresh water, and salt water. They are able to survive for several hours at 100°C (1–4).

C. botulinum produces the most potent known neurotoxin. A single gram of crystalline toxin, whether dispersed or inhaled, would kill more than one million people. The lethal toxin dose for humans is not known, but it is presumed that 0.09–0.15 µg of toxin A, absorbed intravenously or intramuscularly, 0.70–0.90 µg, absorbed by inhalation, and 70 µg, absorbed orally are lethal for a 70-kg human (2). However, this neurotoxin is a fragile protein that easily denatures. It is heat-labile and inactivated in less than five minutes at temperatures above 85°C (1,3,5).

Botulinum toxin is highly neurotrophic. It is introduced in the human body from a mucosal surface (gastrointestinal tract or lung) or a wound and rapidly reaches the bloodstream. It binds to nerve-ending receptors, causing irreversible blockage of cholinergic transmission in all ganglionic synapses, post-ganglionic parasympathetic synapses, and neuromuscular junctions. This binding ultimately results in an acute, afebrile, symmetric, and descending flaccid paralysis and autonomic nervous system dysfunction (1,3).

Ophthalmic signs and symptoms are among the very earliest and most persistent manifestations. They include disturbances of the intrinsic and extrinsic ocular musculature that produce dilated, non-reactive pupils, accommodative paralysis, ptosis, diplopia, decreased lacrimation, nystagmus, and extraocular muscle palsies (1–3,6).

Although the medical literature on botulism is vast (3), most reports that document ophthalmic manifestations are based on single cases. The purpose of this study was to analyze the epidemiology and clinical features of botulism in a single community with an emphasis on ophthalmic findings.

METHODS

Patients were accrued from the database of the Statistics Department of São João Hospital, a general hospital in...
the city of Porto in northern Portugal. We drew from a list of patients admitted to the infectious diseases department of this hospital with a diagnosis of botulism from January 1998 to January 2003.

During this five-year period, 18 patients were admitted with botulism. We recorded data regarding age, sex, region, mode of referral, source of infection, number of outbreaks, number of persons affected by outbreak, type of botulism, neurotoxin involved, incubation period, ophthalmic and non-ophthalmic manifestations, electromyography, and pulmonary function test results, treatment, and follow-up.

Ophthalmological examinations occurred in seven patients and included determination of distant and near visual acuity, measurement of accommodation by a push-up method using a R.A.F. Near Point Rule (Clement Clarke Ltd, Harlow, United Kingdom), slit-lamp examination, tonometry, ophthalmoscopy, Schirmer test, binocular visual fields, Hess test, and computerized infrared pupillometry.

The diagnosis depended on clinical, epidemiological, and electrophysiological findings and was confirmed in most cases by the detection of C. botulinum neurotoxin in serum or stool or in the suspected food. Toxin determination was performed using a mouse bioassay, inoculating extracts of serum, stool, or suspect food intraperitoneally into mice previously protected with monospecific antitoxin.

RESULTS
Epidemiologic and Demographic Features

Nine outbreaks occurred during this five-year period, and all 18 patients were hospitalized with food-borne botulism. There were no cases of wound or infantile botulism. All patients were admitted to the emergency room of this hospital. During this period, 1,040,682 patients were evaluated and treated in the emergency room of this hospital, 2717 of which were hospitalized in the Infectious Diseases Department. Therefore, botulism infection represented 0.7% of all the hospitalizations in that department during this five-year period.

Two patients admitted themselves to the emergency room, ten were transferred from other hospitals, three were referred by a primary care physician, and three were referred by ophthalmologists. Ten were men, and eight were women, with a mean age of 28.8 ± 9.9 years (range, 10–47 years). The median number of cases per outbreak was 4.7 (±2.9). Seven (78%) of the nine outbreaks occurred in rural areas.

Clinical Features
The latency between ingestion of the suspect food and the first symptoms (incubation period) ranged from 1 to 12 days with a mean of 3.1 ± 2.9 days. Two patients (11%) had ophthalmic manifestations as the initial complaints, and ten patients (56%) had non-ophthalmic manifestations as the initial complaints. In the remaining six patients (33%), ophthalmic and non-ophthalmic manifestations occurred simultaneously.

Blurred near vision was described by all patients (Table 1). Among the seven patients examined by ophthalmologists, impaired accommodation was found in all. Seventeen patients (94%) complained of blurred distant vision, eight (44%) experienced diplopia, two (11%) had dry eye symptoms, and one (6%) mentioned photophobia. Apart from the confirmed accommodative loss, the ophthalmic signs included mydriatic pupils sluggishly reacting to light in 15 patients (83%) and bilateral ptosis in seven (39%) patients. Ocular movements were described in four of the eight patients complaining of diplopia. In three of those four patients, ocular alignment was evaluated by an ophthalmologist, and abnormal alignment and bilateral mild abduction weakness were found in one patient (Case 2 below). Nystagmus was not reported in any patients.

Among non-ophthalmological symptoms (Table 2), dry mouth was the most common (100%), followed by constipation (83%) and dysphagia (72%). Nausea, vomiting, diarrhea, and abdominal cramps were also present. In this cohort, 50% experienced fatigue; only 12% reported urinary retention. No patient had dyspnea.

Clinical Diagnosis
Twelve patients (67%) were initially misdiagnosed as suffering from acute gastroenteritis or food poisoning. In five of the seven patients evaluated by an ophthalmologist, the ophthalmologist made the initial diagnosis of botulism. In the remaining two patients, the clinical diagnosis had already been made by an infectious disease specialist.

Laboratory Tests
In 15 (83%) cases, the neurotoxin was detected in the patients’ serum and was classified as type B in all of them. Neither C. botulinum nor its neurotoxin was found in the

<table>
<thead>
<tr>
<th>TABLE 1. Ophthalmic manifestations</th>
<th>Patients (n = 18)</th>
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<tbody>
<tr>
<td>Blurred near vision</td>
<td>18 (100%)</td>
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<tr>
<td>Blurred distant vision</td>
<td>17 (94%)</td>
</tr>
<tr>
<td>Mydriasis with reduced constriction to light</td>
<td>15 (83%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Ptosis</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>1 (6%)</td>
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patients’ stool. The detection of the toxin in the suspect
foodstuff was achieved in 11 cases (61%). Home-preserved
foods were involved in all of the outbreaks, especially
smoked ham (94%). Only one outbreak was attributed to
the ingestion of homemade sausage. In none of the cases
was the taste or smell of the food altered.

In three (30%) of ten patients who underwent elec­
tromyography (EMG), a pattern suggestive of pre-synaptic
dysfunction was seen. The remaining seven (70%) patients
had normal EMG results. A ventilatory restrictive pattern
was found in only one (6%) patient.

Treatment
Fluid and nutritional support were given in all cases.
Some patients required nasogastric tube feeding or par­
enteral nutrition. High enemas were given to patients with
severe constipation. Oxygen saturation was monitored, and
the oropharyngeal secretions were controlled in all patients.
No patient required tracheal intubation, respiratory support,
or antitoxin administration. Induced emesis or gastric
lavage was not performed in any of the patients because the
exposure to the toxin had occurred several days before
diagnosis.

Clinical Course
Patients were discharged after a mean of 5.7 ± 3.9
days (range, 1–19) and followed in the outpatient infectious
diseases clinic. All showed ocular manifestations at the
time of discharge. The last symptoms to disappear were
constipation and blurred near vision. All patients had fully
recovered after eight weeks.

CASE REPORTS

Case 1
A 42-year-old woman presented with nausea, fatigue,
general weakness, and dizziness starting four days before
admission. One day later, these symptoms were followed
by dry mouth, dysphagia, abdominal cramps, and diarrhea.
Two days later, she experienced blurred near vision, as
well as problems in urinating. Her medical history was
otherwise unremarkable.

The patient was diagnosed as having acute gas­
troenteritis, but because of her visual complaints, an exami­
nation by an ophthalmologist was requested.

On ophthalmologic examination, she had a corrected
distance visual acuity of 20/20 OU, bilateral ptosis of 1 mm,
bilaterally defective accommodation for her age (three
diopters), and 6 mm pupils with sluggish reaction to direct
light. Ocular motility and alignment were normal. The rest
of the ophthalmologic examination was normal. When
asked by the ophthalmologist, this patient confirmed having
ingested homemade smoked ham 24 hours before the onset
of her first symptoms.

She was hospitalized in the infectious diseases
department with the diagnosis of food-borne botulism.
Two days after admission, she displayed dilated, non-reactive
pupils and intermittent diplopia. Schirmer I and II tests were
positive in both eyes. Although inconsistent diplopia was
reported on binocular campimetry, the Hess screen test was
normal. Chest x-ray and electrocardiographic, electromyo­
graphic, and spirometric measurements were unrevealing.

Treatment consisted of supportive care, including
parenteral nutrition, fluid supplementation, and artificial
tears. Her condition slowly improved during the following
few days.

Neurotoxin type B was detected by mouse bioassay
in the patient’s serum and in the suspected source (the ham).
Two months later, she had no ocular findings, and recovery
of the pupillary light response was confirmed by pupil­
lometry (Fig. 1).

Case 2
A 47-year-old man presented to an ophthalmologist
complaining of blurred vision, sudden difficulty in focusing
near objects, and intermittent diplopia, followed by
dizziness, nausea, dysphagia, dry mouth, and constipation
starting two days after the ingestion of a home-prepared
smoked ham.

Ophthalmologic examination showed bilateral ptosis
of 2 mm, 6-mm pupils poorly reactive to light, and bilat­
erally defective accommodation for his age (two diopters).
Ocular movements were normal, but he complained of
horizontal diplopia while performing horizontal versions.
A Hess screen test revealed slight weakness of both lateral
rectus muscles. Slit-lamp examination and ophthalmoscopy
were unrevealing. Schirmer I and II tests were borderline
abnormal.

The ophthalmologist suspected botulism and sent
the patient for an infectious diseases specialist evaluation.
EMG was normal. A mild restrictive pattern was detected on spirometry. The electrocardiogram and the chest x-ray were within normal values. Type B neurotoxin was detected in both the patient’s blood and the suspect smoked ham.

The patient received supportive care, including parenteral fluids, soft diet, and artificial tears. At the time of discharge seven days later, he had recovered substantially. Ophthalmic manifestations were absent six weeks later, and pupillometry was normal (Fig. 1).

**DISCUSSION**

In Portugal, especially in northern rural populations, small family-centered outbreaks of botulism occur because of the tradition of home-preserving some foods, particularly smoked ham, and because of unfamiliarity with the requisites of sterilization (7). In all European countries, food-borne botulism is much more associated with meats, especially ham and sausages, than in the United States (3–5), where the most common cause is the consumption of preserved vegetables, which accounts for 60% of the cases (5,8).

An increase in the occurrence of botulism has been observed in Portugal in recent years. Approximately 0.6 outbreaks per year were reported in the Infectious Diseases Department of this hospital from 1970 to 1979, increasing to 2.0 outbreaks per year from 1980 to 1989 and to 2.1 outbreaks per year from 1990 to 2000 (9). A median of 3.0 cases per outbreak was registered in this 30-year period. In comparison, approximately 9.5 outbreaks, with a median of 2.5 cases per outbreak, of food-borne botulism occur annually in the United States (8), a country with 29-fold greater population than Portugal. According to the data published by the Portuguese Governmental Center for Disease Control (Direccão Geral de Saúde) (10), 33 cases were identified in Portugal between 1996 and 2000, and 52% of them occurred in the northern part of the country.

Fortunately, the outbreaks of botulism in Portugal are usually mild, treatable with supportive care measures, and rarely requiring the use of antitoxin therapy. In a 30-year review from 1970 to 2000, 44 outbreaks with a mean of three patients per outbreak, were registered by the Infectious Diseases Department of this hospital (9). A total of 137 patients were affected, 85 of them needing hospitalization. In only one patient was antitoxin administered. Type B toxin was by far the most frequent toxin detected (70%); only two outbreaks were caused by type E toxin. All patients recovered completely. As in other European countries, where type A toxin is rare, the severity of the disease is usually low, probably because of implication of a relatively less potent toxin. In countries where the more aggressive type A toxin prevails, such as the United States, the case-fatality ratio is higher, although it has decreased from 60% to 15% over the last 50 years (8).

The incubation period of food-borne botulism varies with the amount of toxin ingested and absorbed, generally ranging from 18 to 36 hours (4). Many patients first have gastrointestinal symptoms, probably because of locally acting toxin (5), before the onset of neurological manifestations. The upper cranial nerves seem to be affected first, resulting in early intraocular and extraocular ophthalmoplegias. Later manifestations are associated with damage to the lower cranial nerves and the motor neurons to the somatic muscles.

Ophthalmic manifestations are an almost universal finding in botulism, but most of the published literature is not authored by ophthalmologists or found in ophthalmology journals (3). Clinical examination and diagnosis are generally made by non-ophthalmologists, so the reported incidence of ophthalmic findings may be unreliable and not...
quantified. As an example, impaired accommodation is not measured and is generally described as difficulty focusing on a near point. Ocular motility and decreased lacrimation are also not documented frequently. In this study, only seven (39%) of the 18 patients were examined by ophthalmologists, so that full documentation of the ophthalmic findings may be lacking.

As in previous reports, we found that blurred near vision was the most frequent symptom, occurring in all patients. We presume that this complaint is consequent to impaired accommodation because it was confirmed in all seven patients examined by ophthalmologists. A greater frequency of mydriasis was found than in earlier reports (83% versus 44% (2) and 47% (11)), whereas a smaller percentage of ptosis was found (44% versus 49% (11) and 73% (2)). A previous study (11) found a greater frequency of lateral rectus weakness (98%) than we did.

A previous report (11) found that certain ocular signs predict disease severity. Thus, 8 (73%) of 11 patients displaying medial rectus paresis, ptosis, and dilated pupils later experienced respiratory insufficiency, whereas only 1 (3%) of 34 with fewer than three of these findings did so ($P = 0.000006$; Fisher exact test, two-tailed) (11). This study also found that when ventilatory failure did develop, it did so 12 hours after the ophthalmic abnormalities were recorded.

There are reported cases of tonic pupils in botulism (12,13), which could be produced by the action of the toxin at the ciliary ganglion, the neuromuscular junction to the ciliary muscles or pupillary sphincter, or a combination thereof. Rapid quivering eye motions, observed during attempts at refixation of laterally placed objects, are also reported in some patients (6,14,15).

Gastrointestinal symptoms, such as nausea, vomiting, abdominal cramps, and diarrhea, occur before neurological signs and resolve rapidly. Autonomic dysfunction manifested by dry mouth and dilated pupils, followed by diplopia, ptosis, dysarthria, dysphagia, and descending, symmetrical flaccid muscle paralysis are the most prominent features of the disease. Apyrexia and a normal consciousness are features to be remembered in the differential diagnosis.

Diseases most often confused with botulism include acute gastroenteritis, the Guillain-Barré syndrome (GBS), myasthenia gravis, and stroke involving the basilar artery. Initial vomiting and diarrhea can mimic acute gastroenteritis or other forms of food poisoning, but their latency is shorter in gastroenteritis and food poisoning than in botulism. Extreme dry mouth, redness of oral mucosa, and sore throat frequently lead to a misdiagnosis of acute pharyngitis. The presence of visual complaints and other cranial nerve impairment may lead to a misdiagnosis of diphtheria. The history of a previous viral illness, the presence of sensory symptoms, and an increased cerebrospinal fluid protein value would support a diagnosis of GBS. Myasthenia gravis can be differentiated by the finding of muscular fatigability during exercise and by a positive response to edrophonium chloride testing. Stroke usually causes lateralizing signs. Allergic reactions to medications, organophosphate insecticide poisoning, and psychiatric disease can also simulate botulism.

Clinical diagnosis should be supported by a pertinent epidemiologic investigation, but it can be challenging when isolated cases occur. In these cases, involvement of the ophthalmologist may be decisive for a timely diagnosis, as has been shown in this study. Dynamic pupillometry is a useful adjunctive tool to analyze the parasympathetic pupillary light.

As the most poisonous substance currently known, botulinum toxin poses a major bio-weapon threat. In fact, its extreme potency and lethality, ease of production, transport, and elicitation of prolonged intensive care of affected persons encourage its use in bioterrorism, as has already been attempted (2). An aerosolized or food-borne botulinum toxin weapon could cause mass destruction of human life, but there are still some constraints for concentrating and stabilizing the toxin for aerosol dissemination (2). The traditional concept of food-borne botulism, usually associated with home-preserved foods, has expanded, now including commercially processed foods served in public eating places (8) and enlarging the target population in a bioterrorist attack.

There are several features of an outbreak that suggest an intentional release of toxin: 1) large number of affected patients; 2) multiple simultaneous outbreaks without a common source; 3) outbreaks with a common geographic factor (airport, hotel, or workplace); and 4) outbreaks with unusual toxin types C, D, F, G, or E unassociated with aquatic food (2). A detailed dietary, travel, and activity history should be taken, including questions about other persons with similar symptoms.

If unintentional or intentional outbreak is suspected, the clinician should immediately refer the patient to a hospital with an intensive care unit and contact an infection control practitioner and local and state health departments for prompt epidemiological investigation.

Our study shows that the diagnosis of botulism is likely to be made by a health care professional familiar with its clinical manifestations. Because ophthalmic manifestations are usually prominent, the contribution of an ophthalmologist can significantly hasten the correct diagnosis of this potentially lethal disease. In Portugal, botulism usually presents itself in mild form, but in countries with more aggressive forms, like the United States, early detection is critical to reduce morbidity and mortality.
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Ocular Ischemic Syndrome After Occlusion of Both External Carotid Arteries

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Abstract: The ocular ischemic syndrome (OIS) has been reported in association with high-grade stenosis or occlusion of the common carotid artery (CCA) or internal carotid artery (ICA) but never with high-grade stenosis or occlusion of the external carotid artery (ECA) alone. We describe two patients who developed OIS with bilateral occlusion of the ECAs yet patent CCAs and ICAs. In one case, unilateral OIS followed consecutive bilateral carotid endarterectomies. In the other case, OIS developed spontaneously OU but was exacerbated in one eye after ipsilateral carotid endarterectomy (CE) in the setting of pre-existing contralateral ECA occlusion. In some individuals, the ECA is the primary source of arterial blood flow to the eye. Because of this fact, the endarterectomy surgeon must avoid causing ECA occlusion by meticulously removing not only the ICA plaque, but also the entire ECA plaque.


T he ocular ischemic syndrome (OIS) has been reported in association with high-grade stenosis or occlusion of the common carotid artery (CCA) or internal carotid artery (ICA) (1–8). Yet the external carotid artery (ECA) may occasionally be the principal source of blood flow to the orbit and eye especially if there is hemodynamically significant CCA or ICA stenosis (9). The OIS has not been reported in association with occlusion of the ECA when the CCA and ICA are patent.

We describe two patients who developed OIS in association with proximal bilateral ECA occlusion demonstrated on cerebral angiography. In both cases, cerebral angiography did not show high-grade stenosis or occlusion of the CCAs or ICAs. We hypothesize that bilateral occlusion of the ECAs may cause the OIS if the eye is predominantly supplied by the ECA and the endarterectomy surgeon does not meticulously remove the entire plaque stump from that vessel.

CASE REPORTS

Case 1

A 70-year-old hypertensive woman underwent consecutive carotid endarterectomies for asymptomatic carotid stenosis. Sixteen months after the second endarterectomy, and one month after undergoing abdominal aortic aneuysm repair, she developed periocular pain, jaw claudication, facial weakness, and blurred vision on the left side.

Best-corrected visual acuities were 20/40 OD and 20/100 OS. The pupil OD measured 2.5 mm in dim illumination and reacted normally to light, whereas the pupil OS measured 3.5 mm and reacted minimally with an afferent pupillary defect OS. Intraocular pressures were 24 mm Hg OD and 10 mm Hg OS. Ocular ductions and alignment were normal. A left lower motor neuron seventh cranial nerve palsy was present. Iris neovascularization was present in the OS. Ophthalmoscopy disclosed surface wrinkling maculopathy OD and perivenous hemorrhages OS.

Catheter cerebral angiography showed bilateral proximal ECA occlusions. Both ICAs filled normally. The right opthalmic artery (OA) filled from the right OA, but the left OA did not fill (Fig. 1A, A and B). After left ECA patch grafting and stenting, angiography demonstrated ample flow in the ECA; the left OA filled via branches of the ECA (Fig. 1C). The patient's periocular pain and jaw claudication resolved completely within days. The seventh nerve palsy resolved within months. However, she developed markedly increased intraocular pressure OS, presumably as the result of restored blood flow to the ciliary body, which could now produce a more normal volume of aqueous, its exit from the eye blocked by angle closure from neovascular glaucoma. Cyclocryotherapy returned the intraocular pressure to the normal range, and iris neovascularization and...
venous stasis retinopathy regressed several months after panretinal photocoagulation.

**Case 2**

A 70-year-old man developed blurred vision in the OD and, within a week, in the OS as well. He had diabetes mellitus, hypertension, hyperlipidemia, and arteriosclerotic peripheral vascular occlusive disease.

Examination elsewhere disclosed hand movements vision OD and light perception OS. In the OD, ophthalmoscopy showed ischemic retinal whitening; in the OS, it showed pallid optic disc swelling.

Brain MRI showed many small T2 white matter high-signal abnormalities consistent with small vessel occlusive disease. Magnetic resonance angiography (MRA) showed occlusive disease of the left ECA but no significant stenosis of other neck vessels. A right temporal artery biopsy showed arteriosclerosis but no arteritis.

As a desperate measure, a right carotid endarterectomy (CE) was performed, despite the lack of convincing MRA evidence of hemodynamically significant cervical carotid stenosis. Several days later, the patient developed a large area of brawny skin necrosis in the right frontal scalp region (Fig. 2), decreased sensation in the first division of the right fifth cranial nerve, no light perception binocularly, complete ptosis of the right upper lid (Fig. 3), and complete ophthalmoplegia of the OD (Fig. 4). Both pupils measured 6 mm and were unreactive to light. The right cornea was...
opacified with Descemet folds (Fig. 5). Intraocular pressures measured 6 mm Hg OD and 7 mm Hg OS. In the OS, ophthalmoscopy revealed pallid disc swelling.

Catheter cerebral angiography showed non-filling of both ECAs, non-stenosing atherosclerosis of both ICAs, non-filling of the right ophthalmic artery, and filling of the left ophthalmic artery (Fig. 6). A second temporal artery biopsy, performed on the left side, failed to show arteritis.

**DISCUSSION**

Our two patients manifested the OIS in the setting of bilateral ECA occlusions and adequate caliber CCAs and ICAs. In Case 1, bilateral ECA occlusion followed consecutive carotid endarterectomies. The left OA did not fill, presumably because it had depended on the left ECA. The patient developed left OIS. The right OA filled from the right ICA, preserving adequate blood flow to the eye and preventing OIS. In Case 2, after the patient had developed OIS bilaterally, left ECA stenosis was found by MRA. After a right CE, OIS worsened in the OD. Catheter angiography revealed bilateral ECA occlusions with patent ICAs. The left OA filled from the left ICA; the right OA did not fill. We do not know if CE produced a right ECA occlusion that was not evident preoperatively on MRA.

We presume that OIS developed because the eyes of our two patients depended on arterial blood predominantly from the ECA, not the ICA, which remained patent throughout. OIS has been documented in CCA (1–4) and ICA (5–8) occlusive disease, but not in ECA occlusive disease alone. The ICA is usually the main feeder of the ophthalmic artery, but some autopsy dissections have disclosed that the ECA is the principal supply line (Fig. 7) via angular, middle meningeal, lacrimal, or anterior ethmoidal branches (9). Notably, in lower animals like deer and antelope, the eye and orbit are supplied entirely by a branch of the ECA (10) (Fig. 8).

Because of extensive cross flow between the two ECAs, occlusion of one ECA would be unlikely to cause the OIS. In our two patients, occlusion of both ECAs was present. As in our Case 1, this phenomenon may occur iatrogenically when the ECA plaque is incompletely removed during carotid endarterectomy (CE). A common surgical approach in CE is to concentrate on meticulous plaque removal in the CCA and ICA with the assumption that residual plaque and stenosis of the ECA is inconsequential (11,12). This assumption may prove problematic in patients who develop stump emboli that flow into the ICA from an occluded ECA and in patients whose eyes depend on flow from the ECAs.

Iatrogenic ECA occlusion after endarterectomy could arise in one of two ways (Fig. 9). The more common way is through unintentional fracturing of the ECA plaque. The less common way is through incomplete remove of the distal portion of the ECA plaque. In either case, ECA stenosis may be aggravated, producing turbulent flow that
may lead to ECA thrombosis or thromboembolism from the occluded stump back into the ICA.

To avoid ECA occlusion, the endarterectomized vessel must be carefully inspected to assure adequate plaque removal before and after arteriotomy closure. Before arteriotomy closure, use of the operating microscope or loupe illumination and magnification will facilitate a thorough removal of plaque. ECA “eversion endarterectomy” (wherein the CCA just below the bifurcation, or the ECA just above the bifurcation, is transected and “everted” or unrolled in a caudal-cephalad fashion) may also be helpful in removing the most distal ECA plaque. After arteriotomy closure, the removal of plaque should be sufficiently distal so that palpation will reveal an increased pulse in a compressible ECA without any residual palpably non-compressible plaque. After closure of the arteriotomy, an intraoperative micro-Doppler probe is also useful to assess adequacy of flow in the ECA. After the use of the standard longitudinal endarterectomy incision, if the plaque fractures too proximally and the ECA cannot be adequately everted over it to allow for ECA plaque removal, then a separate linear incision in the ECA, or a “Y” incision from the CCA into the ECA, is required to complete the endarterectomy.
FIG. 8. Circulation to the eye and orbit in the antelope (modified from Reference 10). In this animal, as in many others, the ECA is the principal source of the arterial supply of the eye and other orbital structures. The ECA gives rise to the maxillary artery, which later forms an orbital rete (net), one branch of which is the ciliary artery, which supplies the eye.

REFERENCES


FIG. 9. Carotid endarterectomy techniques. In the correct technique (left), the entire ECA plaque is removed. In the incorrect technique (right), only the proximal portion of the plaque is removed, leaving an ECA stump that promotes occlusive thrombosis or embolism.

Recognition of Objects in Non-Canonical Views: A Functional MRI Study

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Background: The neural correlate of object recognition in non-canonical views is uncertain, but there is evidence for involvement of neural pathways, possibly separate from those used for object recognition in canonical views.

Methods: Boxcar functional MRI (fMRI) techniques were used to detect neural activity while eight normal subjects were instructed to identify digital photographs of objects in non-canonical and canonical orientations.

Results: The right angular gyrus, the left inferior temporal gyrus, and the right cerebellum showed significant fMRI activity during non-canonical as opposed to canonical viewing.

Conclusions: Subjects recognizing objects in non-canonical orientations engage in a process separate from, or in addition to, the process used in recognizing objects in canonical orientations.


Objects appear in various orientations in the natural environment. However, because of shape, gravity, and the viewer's position, they are often seen in only a limited number of orientations. Such standard orientations can be described as canonical, whereas unusual orientations can be described as non-canonical. Healthy subjects have been shown to take longer to process and identify objects in non-canonical positions than in canonical ones (1,2). When compared with controls, patients with right posterior cerebral hemisphere lesions have demonstrated difficulties in identifying common objects in non-canonical positions (3–5). Patients with Alzheimer disease have been shown to have more difficulty with this task as well (6). This information suggests that processing objects in non-canonical orientations uses a pathway either separate from, or in addition to, traditional object recognition. The exact nature of these separate neural pathways has not been clarified (1,7).

In normal subjects, bilateral occipital cortical processes have been implicated in initial stages of object recognition (8–10) and object shape processing (11). However, the right posterior cortex has been implicated clinically in impaired recognition of objects in non-canonical views (3–5).

One cognitive process possibly involved in the recognition of objects in non-canonical orientation is mental rotation. Functional MRI (fMRI) studies have shown a wide variety of correlates implicated in the mental rotation of abstract objects (12–15) and alphanumerical characters (16,17). These studies have reported activation of a variety of areas, including those within the parietal, frontal, and occipital lobes. The results of one recent fMRI study (18), in which abstract computer-generated figures were used, suggested that mental rotation and recognition of objects in different views used different neural pathways.

Distinct from mental rotation is a three-dimensional model (19) in which subjects are believed to store images based on geometry and volume. Marr (19) suggests that each physical object has minor and major axes, and these axes are important in deriving the geometry of an object and then matching it to a subject's stored mental image. Under these circumstances, non-canonical perception is proposed to be more difficult if the major axis of the object is obscured. The study of Lange et al (20), however, provided evidence that axes of symmetry and elongation play relatively minor roles in object identification.

Warrington and James (21) observed that the angle of view and recognition were not always related, leading to a model based on the distinctive features of an object. Distinctive features refer to unique properties of the contours of the object, and in this model, the spatial relationship of one feature to another help identify the
orientation and identification of the object. With further rotation of an object away from a canonical view, more of these features would be obstructed. In related models, Hummel and Biederman (22) proposed that recognition of objects in different views depends on a binding of analyses of individual parts, whereas Biederman and Gerhardstein (23) suggested that this process was possible when all views of an object contained the same “geon” structural elements such as straight edges and curved surfaces. Alternatively, Edelman and Duvdevani-Bar (24) theorized that objects can be recognized by a relatively small number of reference shapes.

It may be that components of each of the above models are used in general object recognition. Davidoff and Warrington (5) reported a patient who exhibited significant difficulties in recognizing parts of an object but could still recognize the same object in whole form in a canonical orientation. This observation suggests that the recognition of objects in canonical positions is not based on recognizing individual features but on a broader form. Distinctive features may be more important in the recognition of objects in a non-canonical orientation.

There are many explanations as to why it would be more efficient to store minimal canonical images and evaluate accordingly. First, the process requires minimal memory space. One need only store a common view or a few common views and then use cortical processing to obtain alternative views. Second, the opportunity does not exist to view every object encountered from all possible orientations. The ability to process objects at non-canonical orientations allows for the use of previous visual knowledge at a much faster pace when presented with new stimuli.

Using fMRI paradigms and digital photographs of common objects, this study aims to identify neural pathways involved in non-canonical identification. Photographs are more realistic than computer-generated images and drawings because they include cues such as depth and shadow. Because the recognition of objects in non-canonical orientations is a natural behavior, it is important that the task be as similar to the natural environment as possible. There have been positron emission tomography (PET) investigations using drawings of common objects (1,2) and one fMRI study using cropped photographs (25). No functional imaging studies have used photographs of objects in a natural environment.

METHODS

Subjects

We studied eight volunteers, consisting of five men and three women, ranging in age from 22 to 36 years (mean, 26 years). Seven were right-handed, and one was left-handed.

The subjects were paid to participate and received complimentary copies of neuro-anatomical images of their brain. Informed consent was obtained from all subjects about the nature and consequences of the study. The protocol and study were approved by the Children's Hospital of Philadelphia Institutional Review Board.

All subjects were free of abnormal neurologic or ophthalmic histories. Binocular best-corrected visual acuity was at least 20/25, and each subject had normal confrontation visual fields. When required, each subject's manifest refraction or present prescription was used with a non-metallic lens set in a plastic frame (adapted from a Titmus stereo test; Gulden Ophthalmics, Abington, PA). Full spherical and cylindrical correction was provided when necessary.

The subjects' heads were secured firmly with foam padding within the quadrature head coil to discourage motion. Volunteers were instructed to keep their heads still at all times and their eyelids open during the periods of visual stimulation. A mirror was placed above the opening of the head coil and angled at 45 degrees so the subjects could see a ground-glass screen (Resonance Technologies, Van Nuys, CA) placed at their feet. Once the subject was positioned in the MRI bore, dark material was placed on the sides of the bore opening to block the subject's peripheral vision so that only the ground-glass screen was in view.

Stimuli

A digital camera (Nikon Coolpix 990; Nikon, Melville, NY) was used to photograph common objects in non-canonical (98 photographs) or canonical (97 photographs) positions. Non-canonical views were defined as unusual ones—usually foreshortened views. All objects were photographed in black and white without flash when possible. The images were then converted to PICT files using Adobe Photoshop (Fig. 1). MacStim (David Darby, Carlton, Australia), a Macintosh-based program, was used to animate the presentation of the photographs, which were projected onto the ground-glass screen using a PLUS U2-1080 video projector (resolution 1024 × 758).

Black and white photography was chosen as opposed to color photography, which might provide specific cues for recognition. Tanaka and Presnell (26) have labeled objects low color diagnostic (LCD) or high color diagnostic (HCD). Objects classified as LCD were determined to be objects for which color was not a major identifier, whereas objects classified as HCD were determined to be objects where color was a major identifier (such as a banana). Using their findings, objects for which color was a major determining factor were avoided.
Boxcar Paradigm

A total of eight epochs, four alternating pairs of epochs containing objects either canonically or non-canonically oriented, were presented. Each epoch lasted 39.97 seconds, and within each epoch, the duration of the presentation of each image was self-paced by the subject via a fiberoptic, push-button apparatus (Current Design, Philadelphia, PA). The apparatus contained four buttons arranged in a diamond-shaped pattern. After viewing a photograph of one object, subjects were instructed to identify it silently by name. They acknowledged identification by pressing the right button and lack of identification by pressing the left button. With either choice, the program then advanced to the next image. To determine if the subject correctly recognized the object, the task was repeated outside of the scanner, where the subject confirmed aloud the objects’ names in the presence of an investigator.

Accuracy and average reaction times for each task were calculated. In the object identification tasks, a response was scored as incorrect if 1) subjects determined during the experiment that they could not identify the object, or 2) subjects incorrectly identified the object when the task was repeated. Reaction times were calculated, omitting those objects that subjects could not identify because reaction times were considerably longer for these images, and the end point was not object identification but a random time arbitrarily determined by the subjects. Activation that occurred during the processing of non-identified images was included within the functional analysis.

Scanning and Image Acquisition

Imaging was performed using a 1.5 Tesla Siemens Vision Magnetom MRI Scanner system (Siemens AG, Munich, Germany). The magnet was shimmed using a Siemens automatic shimming routine that used first and second order gradients. A “slice prescription procedure” was performed. First, a coronal scout image was obtained, and oblique axial images perpendicular to the midline of this coronal image were prescribed. Subsequently, sagittal images perpendicular to the midline of the oblique axial images were taken. Finally, the 28 oblique axial planes covering the entire brain were acquired for the anatomic and functional images. They were positioned parallel to the anterior commissure-posterior commissure line.

T1-weighted neuroanatomical images were then obtained with a time to recovery (TR) = 800 ms and a time to echo (TE) = 15 ms. Twenty-eight axial slices, each 5 mm thick, field of view (FOV) 240 × 240 mm, and matrix 256 × 256 were acquired. T2-weighted, echo-planar images were acquired in identical planes as the T1 images. Twenty-eight axial slices, with TR = 3.97 seconds, TE = 29 ms, flip angle = 90 degrees, 5 mm thick, FOV 240 mm × 240 mm, and matrix of 64 × 64 (voxel size, 3.75 × 3.75 × 5 cu/mm) were obtained. The boxcar experiment lasted 5 minutes and 35 seconds. A neuroradiologist reviewed the neuroanatomical images of each subject to exclude any abnormalities.

Post-Processing

Images were analyzed on a Sun SPARC workstation (Sun Microsystems Sun System, Santa Clara, CA). The first five scans of each functional experiment were discarded to eliminate magnetic saturation effects. SPM99 (Wellcome Department of Cognitive Neurology, London, United Kingdom) was used to perform slice-timing correction, realignment, spatial normalization, spatial smoothing, and statistical analysis.

Statistical slice-timing correction was performed to account for the delay in the timing of data acquisition.
at different slices (27). To correct for motion, functional images of each subject were then realigned using SPM99 to the first image by a six-parameter (three translations and three rotations) rigid body transformation. The images were then spatially normalized using SPM99 into the anatomical space defined by the Montreal Neurological Institute (MNI). This was accomplished by minimizing the sum-of-squares difference between the functional images and the SPM99 EPI template using an affine and nonlinear transformation. The voxel size was consistently maintained at 3.75 × 3.75 × 5 mm^3.

**Statistical Maps**

Spatial smoothing was performed with an 8 × 8 × 10 mm width at half maximum Gaussian kernel. Statistical parametric maps, based upon the general linear model, were computed at each voxel. High-pass filter, low-pass filter, and global normalization were used. The reference waveform was modified by a hemodynamic response function. Activation during the non-canonical portions was contrasted with that during the canonical portions. Statistically significant areas across subjects were determined using random effects analysis (28), which involved a first-level analysis consisting of statistical parametric maps generated using the general linear model and random field theory, followed by the application of one sample t-test to the individual activation maps as the second-level analysis.

Areas of activation were determined in the following manner: First, significant voxels were identified (threshold \( P < 0.001 \), uncorrected at voxel level), then significant clusters among these voxels were identified (threshold \( P < 0.05 \), corrected at cluster level). These clusters were characterized by the most significant voxel, but local maxima more than 8.0 mm apart from one another within the cluster were also identified. MNI coordinates were then converted to Talairach (29) coordinates using a nonlinear transformation (for \( Z \geq 0 \), \( X' = 0.9900X, Y' = 0.9688Y + 0.0460Z, Z' = -0.0485Y + 0.9189Z \); for \( Z < 0 \), \( X' = 0.9900X, Y' = 0.9688Y + 0.0420Z, Z' = -0.0485Y + 0.8390Z \)). The Brodmann’s Area (BA) of these areas of activation were determined using the Talairach coordinates.

**RESULTS**

Technically acceptable imaging studies and behavioral responses were acquired for all subjects. The eight subjects viewed an average of 19.9 non-canonical images and 23.0 canonical images per epoch (39.97 seconds). Mean reaction times for correctly identified objects were 1.707 seconds for non-canonical images and 1.542 seconds for canonical images (\( t_7 = 1.562; P = 0.162 \)). Subjects correctly identified a mean 85.8% of the non-canonical photographs and 95.9% of the canonical photographs (\( t_7 = 9.341; P < 0.001 \)). An incorrect identification included both those that the subject could not identify during the test itself and photographs incorrectly identified by the subject after the scan.

When group data (\( n = 8 \)) were compiled using SPM99, and non-canonical and canonical activation were contrasted, three clusters of activation achieved statistical significance (Table 1; Fig. 2). The first cluster was located in the right angular gyrus, extending into the superior occipital gyrus and precuneus (Brodmann areas 39/19; \( P < 0.001 \)). The second cluster incorporated portions of the left inferior temporal gyrus, the left middle occipital gyrus, and the left middle temporal gyrus (Brodmann areas 37/19; \( P < 0.001 \)). The third cluster was located primarily in the right cerebellum (\( P = 0.014 \) (Table 1).

<table>
<thead>
<tr>
<th>Talairach coordinates of principal voxel</th>
<th>Brodmann area</th>
<th>Anatomical position</th>
<th>( P ) (cluster)</th>
<th>Z-score</th>
</tr>
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<tbody>
<tr>
<td>1. 41, −75, 31</td>
<td>39</td>
<td>Right angular gyrus</td>
<td>&lt;0.001</td>
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<tr>
<td>41, −82, 23</td>
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<td>Right superior occipital gyrus</td>
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<td>3.95</td>
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<tr>
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<td>19</td>
<td>Right precuneus</td>
<td></td>
<td>3.34</td>
</tr>
<tr>
<td>2. −59, −59, −10</td>
<td>37</td>
<td>Left inferior temporal gyrus</td>
<td>&lt;0.001</td>
<td>3.59</td>
</tr>
<tr>
<td>−49, −69, −5</td>
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<td>Left middle temporal gyrus</td>
<td></td>
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<td>3.53</td>
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<td>37</td>
<td>Right cerebellum</td>
<td>0.014</td>
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<tr>
<td>41, −44, −15</td>
<td>37</td>
<td>Left inferior temporal gyrus</td>
<td></td>
<td>3.29</td>
</tr>
</tbody>
</table>

Coordinates of three significant clusters in object identification (boxcar) task when the non-canonical viewing condition was contrasted with canonical viewing condition. The first line indicates a cluster maximum; those listed immediately after the cluster maximum are other local maxima within the cluster separated by at least 8 mm. Group analysis (\( n = 8 \), Fig. 2).
DISCUSSION

Our experiments identified regions in the brain more active while subjects recognized objects in non-canonical views than while they identified objects in canonical views. These areas were BA 39/19 in the right angular gyrus region (parietal lobe), BA 37/19 in the left inferior temporal gyrus region (temporal lobe), and the right cerebellum. Why were these areas more active while subjects identified objects in non-canonical views than in canonical ones? Of the areas found to be active, BA 37/19 in the left inferior temporal gyrus region is most often implicated in object recognition. One explanation for this increased activation during non-canonical recognition is that an alternate process in non-canonical recognition is used that actually relies more on object recognition pathways than does canonical recognition. Another explanation could be that the task of identifying objects in non-canonical orientations is simply more difficult, leading to greater levels of activation. However, the average times that elapsed before subjects recorded responses in non-canonical and canonical conditions were not significantly different ($P = 0.162$). This suggests that the difficulty of the two tasks was not as critical as the process itself.

Activation of the other areas in the parietal lobe and cerebellum may be the result of recruitment of specialized visual spatial pathways, as discussed above, for recognition of objects in non-canonical views. These areas may not be active during recognition of common objects in more familiar views (1,7,23,24). Clinical studies have demonstrated the existence of separate pathways, particularly in the posterior right hemisphere, which may mediate non-canonical object recognition. For example, when patients with right posterior cerebral lesions were compared with patients with left posterior cerebral lesions of comparable size and position, those with right-hemisphere lesions showed significant impairment when viewing objects in non-canonical views (3). Vaina (36) presented a patient who was impaired in non-canonical recognition, presumably as the result of impaired visual spatial processing.

FIG. 2. Significant clusters of activation in object identification task when the non-canonical viewing condition was contrasted with the canonical viewing condition. Activated areas are displayed on a smoothed standard brain. (A) Left hemispheric view shows activation in the left inferior temporal gyrus (arrow). (B) Posterior hemispheric view shows activation in the left inferior temporal and right angular gyrus (arrows). (C) Right hemispheric view shows activation in the right angular gyrus and right cerebellum (arrows). (See Table 1).
of bilateral lesions, right larger than left, involving the temporal-parietal-occipital junction. In Davidoff and Warrington's paper (5), a subject had a large infarct in the temporo-parieto-occipital region of the right hemisphere. Also, Landis et al (4) presented the case of a patient who developed, in addition to other visual defects, anagnosia for real objects seen in non-canonical views. Autopsy revealed an occipitotemporal infarct in the territory of the right posterior cerebral artery.

Other functional imaging studies have attempted to localize the areas responsible for the process of non-canonical identification. Using PET imaging, Kosslyn et al (1) found a variety of clusters, among them the left middle temporal region (BA 37) and the right angular gyrus (BA 39/19), thus complementing our results. Also reported were seven other clusters that reached significance (P < 0.05). Apart from the mode of imaging, our object recognition study differed from that of Kosslyn et al (1) in other ways. First, many extraneous thought processes took place in study of Kosslyn et al (1). Subjects were hearing stimuli, seeing stimuli, determining a match or lack of match, and responding to the match. One would expect to see more areas of activation than in our simpler paradigm. Also, Kosslyn et al (1) used line drawings of objects rather than photographs.

The study most similar to ours is that of Sugio et al (25). In their fMRI experiment, subjects were presented with cropped images of objects in non-canonical and canonical positions. They were asked to identify them silently, so it is not certain whether the subjects were completing the task or not. The authors also compared activation during non-canonical and canonical conditions within predeter-

mined anatomical regions of interest. They found greater activation in the non-canonical viewing conditions than in the canonical viewing conditions for the premotor areas bilaterally and the left superior parietal lobule.

One criticism of our study might be that too many extraneous tasks were required, because subjects were asked to imagine the word mentally and then push a button to confirm identification. The main concern was to avoid priming the subjects while still ensuring that the subject was focused on the task and performing the exercise required. By presenting only a photograph to subjects, priming was eliminated, allowing them to rely on their own mental images of the objects, just as they would in a natural environment. However, it was important to receive an answer from the subjects that confirmed that they were awake and participating fully, because attention to the visual stimulus has been shown to enhance cortical activation (37,38). Any extraneous motion, such as the movement of hands or fingers to indicate answers, was present in both conditions in the boxcar paradigm and should have canceled in the contrast. Finally, the relatively small number of subjects used in this study may limit the generalizability of the results.

Warrington and James (39) suggested that there may be an optional pathway used in object recognition when the standard, more direct route fails to provide recognition. In identifying cortical regions more active during recognition of objects in non-canonical views than those in canonical views, our study supports this hypothesis.

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Benign Essential Blepharospasm: Risk Factors with Reference to Hemifacial Spasm

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Background: To identify risk factors associated with benign essential blepharospasm (BEB) with reference to hemifacial spasm (HFS). Persons with BEB and HFS experience similar physical symptoms, yet the two disorders have different etiologies.

Methods: Patients with BEB (n = 159) or HFS (n = 91) were identified from two large neuro-ophthalmology clinics. Demographic, medical, behavioral, and psychological characteristics were obtained from chart review and a telephonic survey questionnaire.

Results: The average age of BEB and HFS was 66 years. Most patients in both groups were retired, white, and female. BEB patients were more than two times as likely to meet the diagnostic criteria for generalized anxiety disorder than HFS patients (odds ratio, 2.13; 95% confidence interval, 1.22–3.72). There was no difference between the two groups regarding demographics, smoking, a family history of dystonia, Parkinson disease, Bell palsy, Tourette disorder, obsessive compulsive symptoms, history of head trauma, alcohol use, or caffeine consumption.

Conclusions: As compared to HFS, BEB was significantly more often associated with generalized anxiety disorder. Given the similarity of other clinical features of these two disorders, it is reasonable to conclude that anxiety is a cause not a consequence of BEB. Contrary to previous studies, BEB was not associated with obsessive-compulsive symptoms, head trauma, Parkinson disease, Bell palsy, Tourette disorder, or lack of smoking.


Blepharospasm is a bilateral condition characterized by excessive involuntary closure of the eyelids generally caused by spasm of the orbicularis oculi muscles (1–4). Benign essential blepharospasm (BEB), the most common form, is of unknown etiology and is considered a form of focal dystonia. Initially, the spasms are mild and infrequent but symptoms typically progress and are highly disruptive to the patient’s visual activities and quality of life (5–7). Studies on the crude prevalence of BEB suggest that it ranges from 12 to 133 cases per million (8–11). However, valid prevalence estimates are elusive because of underdiagnosis, misdiagnosis, and the absence of population-based data. It does seem, however, that BEB is more common than myasthenia gravis, amyotrophic lateral sclerosis, and Huntington disease (8).

A variety of risk factors have been reported for BEB, including family history of dystonia, head and face trauma, previous eye problems, such as blepharitis or keratoconjunctivitis, other neurological movement disorders (Parkinson disease and Tourette disorder), and the fifth to sixth decade of age (9,10,12–16). Smoking was reported to be associated with a reduced risk of blepharospasm in one study (13). Obsessive-compulsive symptoms have been associated with an increased risk in another study (17). Three previously published case-control studies (13–15) found that having first-degree relatives with some form of dystonia increased the risk for BEB. Although these previous studies provide intriguing candidate ideas about potential causes, their methodological shortcomings limit the ability to generate reasonable directions for etiologic hypotheses. For example, most studies included patients with dystonia, of which BEB comprises a small subset, making it difficult to know whether results are applicable to BEB per se or to other forms of dystonia. Relative risks are
sometimes described as crude rather than adjusted estimates, thereby raising the question about the potential role of confounders in reported associations. Two studies have been published only as abstracts, making it difficult to evaluate results (18,19).

The case-control study is the most efficient design when the disease of interest is rare, as is the case with BEB. In the approach taken here, study cases are defined as persons with BEB (but not other types of dystonia). The “control group” is comprised of persons who have been diagnosed with hemifacial spasm (HFS). The logic underlying selection of this control group is that HFS is characterized by clonic-tonic contractions of the orbicularis oculi muscle with eventual involvement of other muscles on one half of the face, and it shares with BEB patients many symptoms and social consequences because of the involuntary lid closure. However, HFS usually has a known cause (peripheral facial nerve irritation caused by vascular compression), whereas BEB remains idiopathic. Unlike BEB (2,20–23), HFS has not been associated with basal ganglia dysfunction (24). Only once before has BEB been compared with HFS in a small sample study of 26 cases (17).

METHODS

Case Selection

Cases were identified from the clinics of the Department of Ophthalmology, University of Alabama at Birmingham, Birmingham, AL and Vision Partners LLC located in Mobile, AL. These two clinics constitute the most popular tertiary referral centers in the state of Alabama for persons suspected of having BEB or HFS. Cases were initially identified from electronic records obtained from clinic visits between December 6, 1999 and December 11, 2002 on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) codes 333.81, 333.82, and 333.83 (blepharospasm, orofacial dyskinesia, and spasmodic torticollis, respectively). Charts containing these codes were then abstracted to confirm the diagnosis of BEB or HFS and to collect selected demographic characteristics. In addition to having either of these diagnoses, subjects had to be at least 19 years of age. The study design and procedures were approved by the Institutional Review Board of the University of Alabama at Birmingham.

Survey Questionnaire

Persons deemed eligible after chart review were contacted by letter describing the study and later by telephone by the research interviewer (KS). Willing participants gave verbal consent and were asked a series of questions by telephone to collect information regarding socio-demographic, behavioral, medical, and psychological characteristics from participants. Socio-demographic characteristics were collected with standard items addressing age, sex, race, education, marital status, total annual family income, and employment status. Behavioral risk factors were assessed through questions concerning cigarette smoking, alcohol use, and caffeine intake. Health history information was obtained from questions regarding whether the respondent had ever had various chronic and acute conditions and surgeries, head trauma, or certain neurological conditions (Bell palsy, Parkinson disease, or Tourette disorder) or a family history of these conditions. General health was assessed by the number of chronic medical conditions reported on a standard questionnaire (25). The number of surgeries in the previous three years was also reported.

The telephone version of the Short Portable Mental Status Questionnaire was used to assess cognitive status (26,27). Obsessive-compulsive symptoms were assessed using the University of Hamburg Obsession-Compulsion Inventory (28). The presence of a generalized anxiety disorder was evaluated by asking about the presence of six symptoms during the past six months, as described in the Diagnostic and Statistical Manual of Mental Health, fourth edition (DSM-IV) (29). The presence of at least four symptoms was necessary to meet criteria for a generalized anxiety disorder.

A research interviewer (KS) experienced in the administration of telephone questionnaires administered the survey. The interviewer was not masked as to the diagnosis of the participant. If the participant was unavailable during the initial phone call, up to four subsequent phone calls were attempted on different days and at different times during the day to maximize the chance of contact.

Statistical Analysis

Comparison between the demographic and medical characteristics of the two patient groups was performed using t tests and \( \chi^2 \) tests for continuous and categorical variables, respectively. The Kruskal-Wallis test was used to compare the two groups with respect to continuous variables that did not meet the assumptions for the \( t \) test. For selected risk factors, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. \( P \)-values of \( \leq 0.05 \) (two-sided) were considered statistically significant.

RESULTS

Of the 347 subjects initially identified by ICD-9-CM codes to be eligible, 250 completed the telephone questionnaire. Ninety-seven subjects did not complete the questionnaire for the following reasons: 36 could not be contacted by telephone, 27 refused to participate, 13 were
### TABLE 1. Demographic, health behavior, medical, and psychological characteristics among benign essential blepharospasm (BEB) and hemifacial spasm (HFS) cases

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>BEB (n = 159)</th>
<th>HFS (n = 91)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years), mean (SD)</td>
<td>65.5 (11.6)</td>
<td>66.3 (12.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Men</td>
<td>44 (27.7)</td>
<td>34 (37.4)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>115 (72.3)</td>
<td>57 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>White</td>
<td>147 (93.0)</td>
<td>79 (86.8)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>11 (7.0)</td>
<td>12 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Less than high school</td>
<td>23 (14.5)</td>
<td>11 (12.1)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>55 (34.6)</td>
<td>30 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>36 (22.6)</td>
<td>19 (20.8)</td>
<td></td>
</tr>
<tr>
<td>College or higher</td>
<td>45 (28.3)</td>
<td>31 (34.1)</td>
<td></td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Married</td>
<td>103 (64.8)</td>
<td>57 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Non-married</td>
<td>56 (35.2)</td>
<td>34 (37.4)</td>
<td></td>
</tr>
<tr>
<td>Income, n (%)</td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Less than $20,000</td>
<td>46 (30.1)</td>
<td>21 (23.9)</td>
<td></td>
</tr>
<tr>
<td>$20,000-$39,000</td>
<td>47 (30.6)</td>
<td>28 (31.8)</td>
<td></td>
</tr>
<tr>
<td>$40,000-$49,000</td>
<td>14 (9.2)</td>
<td>12 (13.6)</td>
<td></td>
</tr>
<tr>
<td>More than $50,000</td>
<td>46 (30.1)</td>
<td>27 (30.7)</td>
<td></td>
</tr>
<tr>
<td>Current employment status, n (%)</td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Currently employed</td>
<td>55 (34.8)</td>
<td>34 (37.4)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>83 (52.5)</td>
<td>52 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Disabled</td>
<td>19 (12.0)</td>
<td>5 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>1 (0.6)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Health behavior characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, now or in past (%)</td>
<td>58 (36.5)</td>
<td>41 (45.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoker, now (%)</td>
<td>18 (11.3)</td>
<td>5 (5.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pack/years cigarette smoking, mean (SD)</td>
<td>8.16 (22.0)</td>
<td>7.90 (16.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Pack/years cigarette smoking, mean (SD), median</td>
<td>0</td>
<td>0</td>
<td>0.37</td>
</tr>
<tr>
<td>Alcohol consumer (%)</td>
<td>90 (65.2)</td>
<td>56 (70.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Ounces of alcohol/week, mean (SD)</td>
<td>6.47 (24.8)</td>
<td>5.33 (18.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ounces of alcohol/week, median</td>
<td>0</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Caffeine consumption (in mg), mean (SD)</td>
<td>167.80 (173.57)</td>
<td>193.39 (230.24)</td>
<td>0.36</td>
</tr>
<tr>
<td>Caffeine consumption (in mg), median</td>
<td>133.0</td>
<td>127.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Medical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of medical conditions, mean (SD)</td>
<td>4.16 (2.39)</td>
<td>3.71 (2.09)</td>
<td>0.14</td>
</tr>
<tr>
<td>Surgical procedure in previous 3 years, n (%)</td>
<td>73 (45.9)</td>
<td>41 (45.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Head trauma, (%)</td>
<td>53 (33.3)</td>
<td>30 (33.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Family history of neurological conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blepharospasm or focal dystonia, n (%)</td>
<td>9 (5.66)</td>
<td>5 (5.49)</td>
<td>0.96</td>
</tr>
<tr>
<td>Bell palsy, n (%)</td>
<td>11 (6.92)</td>
<td>10 (10.99)</td>
<td>0.26</td>
</tr>
<tr>
<td>Parkinson disease, n (%)</td>
<td>9 (5.66)</td>
<td>4 (4.40)</td>
<td>0.77</td>
</tr>
<tr>
<td>Tourette disorder, n (%)</td>
<td>1 (.01)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Continued
TABLE 1 (Continued). Demographic, health behavior, medical, and psychological characteristics among benign essential blepharospasm (BEB) and hemifacial spasm (HFS) cases

<table>
<thead>
<tr>
<th></th>
<th>BEB (n = 159)</th>
<th>HFS (n = 91)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (BEB or HFS) in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of self-reported symptoms, mean (SD)</td>
<td>13.28 (10.2)</td>
<td>13.47 (9.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>Duration of physician diagnosis, mean (SD)</td>
<td>9.85 (6.6)</td>
<td>8.37 (6.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Psychological characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized anxiety disorder (%)</td>
<td>71 (44.7)</td>
<td>25 (27.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Obsessive-compulsive symptoms, (%)</td>
<td>60 (37.7)</td>
<td>28 (30.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mental status, mean (SD)*</td>
<td>0.56 (0.67)</td>
<td>0.62 (0.68)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

* from Short Portable Mental Status Questionnaire.

decesed, 4 had impaired mental status, 5 were too ill to participate, 4 had been surgically cured of HFS, 3 had hearing impairment, 2 requested to be contacted later but were not reachable, 1 ended the interview without finishing because of difficulty with Parkinson disease, 1 declared that the interview had lasted too long and decided to quit, and 1 had too poor a command of English to be understood. Ultimately, 159 BEB cases and 91 HFS controls were enrolled in the study. Those who refused the invitation to enroll were not different from the enrollees with respect to age, sex, and race, and the proportion of refusers who had BEB versus HFS was similar to that of the enrollees.

The average age of both groups was 66 years (Table 1). Women comprised most of BEB (72.3%) and HFS (62.6%) subjects. Whites comprised 93.0% and 86.8% of the BEB and HFS groups, respectively. The two groups were similar with respect to the distribution of educational level, marital status, and income level. Regardless of group, slightly more than 50% of the patients were retired, approximately 33% were employed, and the remainder was disabled or unemployed. There was no difference between groups with respect to current smoking status or having ever been a smoker or in alcohol or caffeine consumption.

BEB cases were more than two times more likely to meet the diagnostic criteria for generalized anxiety disorder than HFS controls (OR, 2.13; 95% CI, 1.22–3.72).

The two groups did not differ with respect to the number of chronic medical conditions, history of head trauma, family history of neurological conditions (other focal dystonias, Bell palsy, Parkinson disease, or Tourette disorder), or disease duration. The two groups were similar with regard to mental status score and obsessive-compulsive symptoms.

DISCUSSION

The most important result of our study is that patients with BEB had a significantly higher frequency of generalized anxiety disorder than did patients with HFS. Previous studies have not found such an association when BEB patients were compared to normal controls (30), to a small sample of HFS patients (17), or to population-based reference values (31,32,34). Whether generalized anxiety disorder caused, resulted from, or may be concomitant with BEB cannot be determined from this study. However, given the similarity in the physical symptoms and impairments experienced by BEB and HFS patients, a similar frequency of patients in both groups would be expected to have an anxiety disorder if it were a consequence. Thus, consideration should be given to the possibility that generalized anxiety disorder has a role in BEB origin. Our results do not confirm earlier reports of an association between BEB and obsessive-compulsive disorder or symptoms (17,35). Previous studies reporting an association had small sample sizes (less than 25 BEB patients each). The larger sample studied here suggests that an association between obsessive compulsiveness and BEB is unlikely.

We suggest the following framework as a hypothesis explaining how generalized anxiety disorder could be involved in the etiology of BEB. Anxiety and stressful situations are known to trigger an acute increase in cortisol levels that subsequently become downregulated during chronic anxiety states (36), resulting in hypocortisolism (36,37). Recently, Pruessner et al. (38) extended the results of previous animal studies reporting a link between stress-related cortisol levels and striatal dopamine levels by demonstrating that a stress-induced increase in cortisol produced a corresponding increase in the release of striatal dopamine in human subjects. According to this line of reasoning, the hypocortisol state induced by generalized anxiety disorder might also induce a proportionally decreased level of striatal dopamine. These factors are linked to BEB by a recent study (39) that demonstrated that a decrease in striatal dopamine would measurably increase the trigeminal blink reflex (TBR), an important component of BEB...
pathophysiology, in an animal model. This relationship is also thought to occur in humans (40). Moreover, TBR excitability is increased by other factors common in BEB (irritative eye conditions such as blepharitis and dry eye (39–44)). Thus, in this hypothetical framework, the development of BEB would involve the merging of several factors that increase the excitability of the TBR, which, in a genetically predisposed individual, could foster the development of BEB. Because not all older persons with this combination of environmental and genetic characteristics develop BEB, additional factors presumably play a role. Neurological kindling, similar to that proposed in epilepsy, alcohol withdrawal, and bipolar disorder, is a possibility, given that BEB is known to worsen over time and become less responsive to treatment.

Insufficient power may have prevented the detection of differences that actually existed between the two groups. Also, the interviewer was not masked to the case or control status of the participant during the telephone survey. Whereas this was not ideal, the interviewer was experienced in performing an objective medical interview and was not privy to the study hypothesis such that any bias the interviewer may have introduced would be minimal.

REFERENCES

33. Deleted.


Recurrent Neuroretinitis in an Adolescent with Ulcerative Colitis

Mohammad Shoari, MD, and Bradley J. Katz, MD, PhD

Abstract: Neuroretinitis refers to an optic neuropathy in which optic disc edema is accompanied by peripapillary or macular hard exudates. Most cases involve a single episode and have no associated systemic abnormalities. In rare instances, neuroretinitis may be recurrent and lead to progressive visual loss. We describe a patient with recurrent neuroretinitis who concurrently developed ulcerative colitis, the first report of this association.


Neuroretinitis refers to an optic neuropathy associated with the unique combination of optic disc edema and peripapillary or macular hard exudates (1). Some cases of neuroretinitis are associated with a systemic disease. Most patients experience spontaneous remission and restoration of normal visual function. In rare instances, patients may suffer recurrent neuroretinitis that results in a progressive loss of visual function. In contrast to single-episode neuroretinitis, recurrent neuroretinitis is thought to be an autoimmune disease. We report a patient with recurrent neuroretinitis who concurrently developed ulcerative colitis. To the best of our knowledge, this is the first report of recurrent neuroretinitis associated with inflammatory bowel disease.

CASE REPORT

A 14-year-old boy presented to an optometrist with acute, painful visual loss OS. Visual acuity was 20/20 OD and 20/200 OS. The patient was referred to our institution four to six weeks after visual loss was first noted by the patient. Visual acuity had improved to 20/15 OD and 20/40 OS.

He had a small afferent pupillary defect and decreased color vision OS. Ophthalmoscopy revealed 360° of optic nerve swelling and mild diffuse pallor OD. The vitreous was quiet. In the OS, the optic nerve was swollen for 360° with a stellate pattern of lipid exudates surrounding the macula. Serologic testing, including complete blood count, angiotensin converting enzyme, B. henselae titer, and B. burgdorferi titer, was within normal limits. Brain computed tomography (CT) scan was normal except for fluid distention of the left optic nerve sheath. Fluorescein angiography was normal OD; angiography OS revealed diffuse optic nerve leakage. Late in the angiogram, leakage was noted from the optic disc toward the fovea. The diagnosis was neuroretinitis. Without treatment, he experienced marked visual improvement OS within several weeks.

One year later, he experienced blurred vision OD. Visual acuity was 20/400 OD and 20/20 OS. Ophthalmoscopy now revealed 360° of optic nerve swelling with obscuration of retinal vessels at the periphery of the disc and at the center of the disc. Exudates were observed tracking from the nerve toward the fovea (Fig. 1). Brain MRI and lumbar puncture were normal. Serologies for cytomegalovirus, coccidioides, cysticercosis, Bartonella, Aurelia, toxoplasma, and toxocara were all negative. He was diagnosed with a second episode of neuroretinitis, hospitalized, and treated with intravenous corticosteroids (250 mg methylprednisolone IV every 6 hours for three days) and an oral taper (60 mg prednisone orally tapered over 11 days). Several weeks later, visual acuity OD had returned to normal and optic disc edema had improved.

Eleven months later, he reported a 4-day history of blurred vision in the OS. Visual acuity was 20/30 OD and 20/20 OS. Ophthalmoscopy revealed an early macular star and recurrent disc swelling OS. He was treated with 1 g methylprednisolone IV daily for three days and prednisone 60 mg/d tapered over 11 days. Five months later, visual acuity and visual fields were stable, and his optic nerve swelling and exudates had completely resolved.

As this most recent attack of neuroretinitis was resolving, approximately three years after his initial attack of neuroretinitis, he developed bloody diarrhea and abdominal cramps. Colonoscopy revealed ascending and transverse...
colon inflammation. The terminal ileum was normal. Biopsies of the inflamed colon were consistent with ulcerative colitis. The patient was treated with azathioprine and mesalazine. His abdominal cramps and bloody diarrhea improved, and the azathioprine dose was reduced.

Within a few months of tapering the azathioprine dose, the patient noted loss of vision OD. Visual acuity was 20/200 OD and 20/60 OS. Ophthalmoscopic examination OD showed optic disc edema with a macular star. Examination of the OS revealed diffuse pallor of the optic disc. Visual field testing revealed superior and inferior arcuate scotomas OU. The dose of azathioprine was increased with periodic monitoring of blood count and liver enzymes. In addition, he was again treated with a 3-day course of intravenous methylprednisolone 1 gm/d followed by methylprednisolone 24 mg/d tapered over six days. Two months later, visual acuity had improved to 20/70 OD and 20/40 OS. He could identify only 1/7 Hardy Rand Rittler (HRR) color plates in OU; automated perimetry showed superior and inferior arcuate defects, enlarged blind spots, and central scotomas OU. Five weeks later, he reported blurred vision in the OS. Acuity was 20/70 OD and 20/200 OS. The optic disc OD showed diffuse pallor without edema. The optic disc OS was diffusely pale and swollen, and a new macular star had appeared. A similar course of IV methylprednisolone with an oral methylprednisolone taper was prescribed.

The patient is currently serving as a missionary and has moved out of state. By report, his visual acuity improved after his most recent corticosteroid treatment, but he subsequently suffered another attack of neuroretinitis in the OD that was treated with a similar course of IV methylprednisolone followed by oral methylprednisolone. His azathioprine dose has been increased from 200 mg/d to 250 mg/d.

**DISCUSSION**

Neuroretinitis was first described by Leber in 1916 as a retinopathy associated with unilateral vision loss, optic disc swelling, and an exudative maculopathy in young healthy patients (2,3). Patients range in age from 9 to 55 years with no gender preference. Visual acuity can range from 20/50 to 20/200 (4). An afferent pupillary defect and decreased color vision are usually present. The most common visual field defects are eccoentral and central scotomas (5). Almost all cases affect only one eye, but bilateral cases have been described. Most patients who develop neuroretinitis do not experience a subsequent attack in the same eye, and only a small percentage of patients who have experienced an attack in one eye subsequently develop a similar attack in the other eye (1). Neuroretinitis often resolves spontaneously (6), and most patients enjoy a full restoration of visual function.

Many inflammatory and infectious conditions have been associated with neuroretinitis, but approximately 50% of cases remain idiopathic (7). There is a growing list of reports of associations with infectious, autoimmune, and neoplastic conditions (4,8). Many of these conditions are treatable, and accurate diagnosis can result in visual rehabilitation. The infectious conditions associated with neuroretinitis are summarized in Table 1.

In contrast to patients with the typical monophasic neuroretinitis, a minority of patients develop a more severe illness with recurrent episodes of neuroretinitis involving the same eye, the fellow eye, or both. This recurrent form of the disease is characterized by a poor visual outcome. The

| TABLE 1. Infectious etiologies of neuroretinitis that have been previously described |
|---------------------------------------|-------------------|
| Unilateral disease                   | Bilateral disease |
| Cat scratch disease                  | Mumps             |
| Lyme disease                         | Lyme disease      |
| Toxoplasmosis                        | Herpes zoster     |
| Toxocariasis                         | Toxoplasmosis     |
| Histoplasmosis                       |                   |
| Hepatitis B                          |                   |
| Leptospirosis                        |                   |
| Mumps                                |                   |
| Herpes simplex                       |                   |
| Salmonella                           |                   |
| Tuberculosis                         |                   |
| Syphilis                             |                   |
| Typhus                               |                   |
cause of this disorder has not been identified and has simply been termed recurrent idiopathic neuroretinitis. Although laboratory testing has not revealed a systemic disease in these patients, some researchers suspect an autoimmune disorder involving the optic disc (4,9,10).

Unlike the favorable prognosis that applies to the monophasic illness, recurrent neuroretinitis is characterized by repeated acute episodes that may lead to progressive and permanent visual loss (11). The incomplete recovery of visual function has been ascribed to permanent damage to the optic nerve, not the macula. In comparison to monophasic neuroretinitis, the evaluation of patients with recurrent disease is almost always unrevealing. Purvin et al (11) have suggested that the most likely cause in recurrent cases is a very discrete and localized form of autoimmune disease. However, recurrent cases have also been associated with toxoplasmosis (12,13), melanocytoma (14,15), and sarcoidosis (16,17). Three cases of neuroretinitis have been described in patients with multiple sclerosis (18), but recurrent neuroretinitis in association with multiple sclerosis has not been reported.

Purvin et al (11) also studied the effects of long-term immunosuppression in patients with recurrent neuroretinitis. They retrospectively reviewed seven patients with recurrent neuroretinitis who were treated with prednisone, azathioprine, or both. The interval between attacks was quite variable in their series, ranging from one month to 9.8 years. For the entire group, the attack rate decreased 72% after initiation of immunosuppressive therapy from 0.58 attacks per year before the initiation of immunosuppressive treatment to 0.16 attacks per year after treatment. They concluded that long-term immunosuppressive therapy was a reasonable approach in these patients.

Our patient with recurrent neuroretinitis eventually developed ulcerative colitis. Ophthalmic complications of inflammatory bowel disease were first reported by Crohn (19) in 1925, and he hypothesized that the two patients he treated probably suffered from keratomalacia and xerophthalmia caused by hypovitaminosis A. In a series of 700 patients with inflammatory bowel disease, 4% of patients had ocular manifestations (20). Ocular manifestations of inflammatory bowel disease include episcleritis, scleritis, uveitis, keratitis, vitreitis, choroidal infiltrates, retinitis, and retinal vascular diseases (20). These manifestations are less severe in patients with ulcerative colitis than in those with Crohn disease (20). A case series reported optic neuritis in five patients with inflammatory bowel disease (21). A single case of bilateral papillitis, retinitis, and hyalitis has also been described in an adolescent with granulomatous ileocolitis (22). To the best of our knowledge, neuroretinitis has not been previously reported in inflammatory bowel disease.

REFERENCES

Primary Melanoma of the Sphenoid Sinus Presenting with a Third Cranial Nerve Palsy

Shannon C. Lynch, MD, Andrew G. Lee, MD, Scott M. Graham, MD, and Patricia A. Kirby, MD

Abstract: An 83-year-old woman presented with right trigeminal paresthesias, upper lid ptosis, and diplopia and was found to have a right third cranial nerve palsy. MRI disclosed a right sphenocavernous mass with speckled high signal on pre-contrast T1 and correspondingly low signal on T2. Endoscopic sphenoidotomy revealed malignant melanoma. The patient underwent radiation therapy with complete and protracted resolution of the palsy. An extensive evaluation for a primary source was negative. The combination of

FIG. 1. Imaging at presentation. (A) Pre-contrast T1 coronal MRI of a mass in the right sphenoid and cavernous sinus with areas of high signal. (B) T2 MRI of the same area shows that the T1 high-signal areas correspond to low-signal areas in the mass. (C) Axial T2 MRI also shows these abnormal signal areas (arrow). (D) Post-contrast axial T1 MRI shows homogeneous enhancement.
high T1 signal and low T2 signal in a mass should suggest melanin. An exceedingly rare condition, this is the first English report of its presentation with a third cranial nerve palsy.


FIG. 2. Pathology of the tumor. (A) Hematoxylin and eosin stain shows large polygonal cells with abundant cytoplasm, large nuclei, and prominent nucleoli. (B) HMB-45 immunohistochemical staining is positive for melanin.

An 83-year-old woman presented with new right upper lid ptosis, diplopia, and a warm sensation in the second trigeminal distribution on the right. She said she did not have a headache. Ocular and medical history was non-contributory. There was no previous personal or family history of cutaneous or systemic malignancy. She was taking one aspirin per day. She was widowed and did not smoke nor drink alcohol.

Visual acuity was 20/30 OD and 20/20 OS. There was almost complete ptosis OD. The pupils measured 4 mm OU in darkness and 2 mm OU in light. There was no relative afferent pupillary defect. There was complete lack of supraduction, adduction, and infrafduction but intact abduction and intorsion OD. The ductions were intact OS. There was a 60 prism-diopter exotropia in primary position. She was hyperesthetic to pinprick in the second trigeminal distribution on the right side of the face and reported a paresthesia “like a warm sensation” in this area. Slit lamp examination showed a cataract OD consistent with 20/30 acuity. The remainder of the ophthalmic examination, including intraocular pressure measurements and ophthalmoscopy, was normal OU. There was no temporal artery tenderness. The neurologic examination was normal. An erythrocyte sedimentation rate and C-reactive protein were normal.

Computed tomography (CT) of the sinuses showed opacification and expansion of the right sphenoid sinus and partial erosion of the posterolateral wall adjacent to the right cavernous sinus. Brain MRI revealed a lesion in the right cavernous and sphenoid sinuses that showed areas of hyperintensity on T1 corresponding to areas of hypointensity on T2 and mild homogenous contrast enhancement (Fig. 1). CT of the chest, abdomen, and pelvis was unremarkable. Complete physical examination was normal.

The differential diagnosis included cavernous sinus meningioma, lymphoma, metastatic cancer, and sphenoid sinus adenocarcinoma. A right endoscopic sphenoidotomy revealed that the sphenoid sinus lesion was covered with a layer of normal mucosa. A subtotal resection and biopsy were performed. The nidus of the mass appeared to be within the wall of the lateral sphenoid sinus, with extension into the adjacent cavernous sinus. The pathology showed an infiltrate of large polygonal cells with abundant cytoplasm. The nuclei were large and vesicular with prominent nucleoli. Immunohistochemistry for melanoma markers S-100, HMB 45, and MART 1 was positive (Fig. 2).

Examination by a dermatologist was negative for cutaneous melanoma. Positron emission tomography (PET) scan showed nonspecific uptake in the right upper abdominal quadrant, but no primary melanoma was identified. This PET scan finding was not believed to be consistent with metastatic melanoma, although it cannot be completely

FIG. 3. Imaging three months after completion of treatment. Pre-contrast axial T1 MRI shows marked reduction in tumor size.
excluded. The patient was treated with 60 Gy of radiation therapy in 30 fractions to the tumor bed with 54 Gy to the sphenoid sinus. Within a few months of treatment, her ptosis had resolved. A repeat MRI three months after treatment showed marked reduction in the size of the right cavernous sinus and sphenoid sinus lesion (Fig. 3). She denied diplopia despite a residual 12 prism-diopter intermittent exotropia. She had significant improvement of her trigeminal paresthesias with resolution of the warm feeling she had described previously. As of her latest visit, eleven months after treatment, she was asymptomatic. MRI showed minimal residual tumor with postoperative changes in the sphenoid sinus, and there was no evidence of metastatic disease. The PET scan was not repeated. The patient was offered but refused colonoscopy. An oncologist examined the patient and decided that, in the absence of any suggestive symptoms, repeated evaluation was not required.

The melanoma in our patient appears to have been primary to the sphenoid sinus. Primary malignant melanoma of the paranasal sinuses is rare. Almost 20% of melanomas (cutaneous and mucosal) originate in the head and neck, but only 1% arise from the sinonasal tract (1,2). The nasal cavity is most frequently affected, followed by the maxillary sinus, ethmoid sinus, frontal sinus, and sphenoid sinus (1). The melanoma is derived from melanocytes that normally migrate as neural crest derivatives in ectodermally-derived mucosa (2,3). In a review of 377 cases of head and neck melanomas (2), the peak incidence was in the fifth to eighth decade. The earliest symptoms were epistaxis and nasal stuffiness (2,4,5). There have been only five reported cases of primary sphenoid sinus melanoma (4–8). Of these, four cases initially presented with neuro-ophthalmic complaints, including diplopia, ptosis, visual field defects, or decreased visual acuity (4,6–8). Each of these patients had spread of the melanoma into the adjacent cavernous sinus (Table 1).

The appearance of melanoma on MRI depends on the amount of melanin in the tumor. Melanotic melanoma often shows a hyperintense signal on T1 and a hypointense signal on T2. Amelanotic melanoma is hypointense or isointense on T1 and hyperintense or isointense on T2.

**TABLE 1. Summary of previously reported cases of primary sphenoid sinus melanoma**

<table>
<thead>
<tr>
<th>Reported cases</th>
<th>Age/sex</th>
<th>Neuro-imaging</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter (1986) (6)</td>
<td>67/F</td>
<td>Unknown</td>
<td>Nasal stuffiness; epistaxis</td>
<td>Excision and radiation therapy</td>
<td>Local recurrence 1.5 years after treatment; alive 2.5 years from presentation</td>
</tr>
<tr>
<td>Shinbordi et al (1988) (4)</td>
<td>67/F</td>
<td>Head CT: isodense with enhancement; Angiography: faint stain</td>
<td>Headache; bilateral decreased visual acuity; anosmia; bilateral CN VI pareses; R CN III, IV pareses</td>
<td>Radiation therapy</td>
<td>Died within 3 months of presentation from respiratory insufficiency</td>
</tr>
<tr>
<td>Busaba (2000) (3)</td>
<td>87/F</td>
<td>Brain MRI: Pre-contrast T1 signal not reported, hypointense on T2; enhancement with Gd</td>
<td>Headache; R decreased visual acuity; R CN VI paresis</td>
<td>Radiation therapy alone</td>
<td>Died 1 year due to metastasis</td>
</tr>
<tr>
<td>Asano et al (2000) (5)</td>
<td>83/F</td>
<td>Head CT: iso- to hyperdense with moderate enhancement; Brain MRI: hyperintense on T1, hypointense on T2, moderate enhancement with Gd; Angiography: transient blush</td>
<td>Headache; epistaxis; pituitary involvement; bilateral decreased visual acuity; anosmia; bilateral CN VI pareses; L CN III, IV, V1, V2 pareses</td>
<td>Supportive treatment only</td>
<td>Died 6 months later from multiple organ failure</td>
</tr>
<tr>
<td>Pino Rivero et al (2004) (2)</td>
<td>56/M</td>
<td>Head CT: iso- to hyperdense; Brain MRI: hyperintense on T1, moderate enhancement with Gd</td>
<td>Headache, R eye pain; R CN VI paresis; R ptosis</td>
<td>Radiation therapy</td>
<td>Still alive 4 years after presentation</td>
</tr>
<tr>
<td>Present case (2005)</td>
<td>83/F</td>
<td>Head CT: isodense; Brain MRI: iso- to hyperintense on T1, iso- to hypointense on T2, mild enhancement with Gd</td>
<td>Headache; R CN III paresis; R V2 paresthesia</td>
<td>Partial excision with radiation therapy</td>
<td>Still alive 15 months after presentation</td>
</tr>
</tbody>
</table>

CN, cranial nerve; CT, computed tomography; MRI, magnetic resonance imaging; Gd, gadolinium; R, right; L, left.
The hyperintense signal intensity seen on T1-weighted images and hypointense signal on T2-weighted images is caused by melanin’s paramagnetic properties (9,10). The differential diagnosis for an increased T1 signal on MRI also includes fat, gadolinium, methemoglobin, proteinaceous fluid, ferritin, copper, immature calcium, magnesium, and manganese complexes.

Surgical resection is the treatment of choice for melanoma (11). However, radiation therapy and chemotherapy, as primary or adjunctive treatments, have also been used with disappointing results (2,11). Immunotherapy with interferon alpha or allogenic vaccine has not yet been sufficiently evaluated (12). Local relapse occurs in more than 50% despite treatment. Distant metastasis can occur and PET scanning is emerging as the diagnostic modality for metastatic evaluation. In comparison to patients with cutaneous melanoma, the prognosis tends to be worse because the tumor is often discovered at a more advanced stage (11). The prognosis seems to be related to the extent and location of the primary tumor and the adequacy of the surgical excision. Although the 5-year survival rate ranges from 14% to 45% for patients with head or neck mucosal melanoma (2,9,11), the 5-year survival rate was 0% for patients with sinus melanoma in one report (2,13–15).

REFERENCES

Abstract: A 90-year-old woman developed an acute left third cranial nerve palsy. Brain imaging revealed a left sphenoid sinus mucocele. Endoscopic marsupialization of the mucocele led to complete resolution of the third cranial nerve palsy.


A 90-year-old woman developed binocular diplopia followed by complete ptosis OS. There were no symptoms of giant cell arteritis. She had had hypertension for ten years and hypercholesterolemia for five years but no history of diabetes. She had had a left carotid endarterectomy several years earlier, hypothyroidism, and osteoporosis. Medications included levothyroxine, lisinopril, nitrindipine, triamterene, hydrochlorothiazide, risedronate, celecoxib, and aspirin.

Visual acuity was 20/20 OU, and confrontation visual fields were normal. Pupils were equal at 4 mm OU with normal reactivity and no relative afferent pupillary defect. Ductions were full OD. The OS would not adduct beyond the midline; supraduction was diminished, but infraduction and abduction were intact. Complete upper lid ptosis was present OS. Exophthalmometric, biomicroscopic, and ophthalmoscopic examinations were normal, as were assessments of trigeminal and facial nerve function.

The diagnosis was left pupil-sparing third cranial nerve palsy. Complete blood count, electrolytes, and glucose were normal. Cholesterol was 140 mg/dL, triglycerides 170 mg/dL, and an erythrocyte sedimentation rate was 23 mm/h.

A brain and orbit MRI scan showed a large non-enhancing mass in the left sphenoid sinus compressing the cavernous sinus (Fig. 1), including the region where the

FIG. 1. (A) Axial bone-windowed CT shows an opacified left sphenoid sinus with thinning and outward bowing of remodeled bone. (B) Coronal T1 MRI shows a large mass in the sphenoid sinus that compresses the cavernous sinus near the point where the left third cranial nerve passes the anterior clinoid process (arrow).
third cranial nerve was passing through. Computed tomography (CT) showed that the mass was expanding the sinus wall and causing remodeling of bone consistent with the effects of a chronic mucocele. Brain magnetic resonance angiography (MRA) was normal.

The patient underwent endoscopic marsupialization of the mucocele. One month after surgery, the third cranial nerve palsy had completely resolved.

Mucoceles are cyst-like lesions lined with respiratory epithelium; retention of mucoid secretions leads to thinning and erosion of the sinus bony walls (1,2). More than half of these lesions are located in the frontal sinuses, with most of the remainder being in the ethmoid sinuses. Sphenoid sinus mucoceles are relatively rare, representing 1% of all paranasal sinus mucoceles (3,4). They usually start unilaterally, but by the time of presentation, the entire sphenoid sinus complex may be opacified and expanded with thinning of its bony walls. The sinus expands anteriorly at the level of the anterior clinoid process where the third cranial nerve bears closest relationship to the sinus (5). Compression of the cavernous sinus may cause exophthalmos and periorcular pain (2,3,6–8). Cranial neuropathies are a feature in as many as 50% of cases (4). The third cranial nerve is the most frequently involved (5). Sparing of pupil function mimics a vasculopathic process in 46.6% of cases (7), as in our patient. Other patients present with periorcular pain and a third cranial nerve palsy with pupilloparesthes that mimics aneurysmal compression (5). In some cases, the third cranial nerve palsy may wax and wane (2). Frontal sinus mucocele has also been reported to cause ophthalmoparesis by extension into the orbit from above (9,10).

Treatment consists of marsupialization of the mucocele, usually resulting in rapid regression of the ophthalmologic manifestations (2). However, optic neuropathy seldom recovers (7).

REFERENCES

Erectile Dysfunction Drugs and Non-Arteritic Anterior Ischemic Optic Neuropathy: Is There a Cause and Effect Relationship?

Sohan Singh Hayreh, MD, PhD, DSc, FRCS, FRCOphth

Abstract: The recent reports of non-arteritic anterior ischemic optic neuropathy (NAION) occurring shortly after ingestion of erectile dysfunction agents have raised the question of whether these agents have a cause-and-effect relationship to NAION. The nature of optic nerve head blood flow and the various factors that influence it, the systemic vascular effects of these agents, and the clinical features of NAION lead me to believe that these agents are contributory factors. Patients with the appropriate risk factors should, therefore, be warned of this possibility and advised to refrain from using these agents.


Since the U.S. Food and Drug Administration (FDA) approved sildenafil citrate (Viagra) on March 27, 1998 to treat male erectile dysfunction, it has become one of the most popular drugs worldwide. More recently, tadalafil (Cialis) and vardenafil hydrochloride (Levitra) have been introduced for the same purpose.

The FDA recently reported visual loss in 38 patients after use of sildenafil and in one patient after use of vardenafil. A Medline search revealed published reports of 15 patients who have developed non-arteritic anterior ischemic optic neuropathy (NAION) soon after the ingestion of sildenafil (1–7), and three patients who developed it after use of tadalafil (8–10). Varied opinions on the cause-and-effect relationship between these drugs and the development of NAION have been expressed by the FDA, the pharmaceutical industry, ophthalmologists, urologists, and other physicians, resulting in considerable confusion in the public mind. For example, in the New York Times, May 29, 2005, Suzanne Trevino, a spokesperson for the FDA, said “We’re not able to specifically say that these 38 cases are a result of the patients taking Viagra.” The same newspaper article quoted Michael Bercowitz, MD, Pfizer’s vice president, as saying, “We’ve studied all our databases right now, and we see no signal of causation with Viagra.” David Moskowitz, an analyst at Friedman, Billings, and Ramsey, is quoted as saying that “It may not be the drug at all; it may be just the patient population that’s experiencing this blindness...We think this was an overreaction.” In the Archives of Ophthalmology, Egan and Fraunfelder (11) have stated that the connection between sildenafil use and the development of NAION does not meet World Health Organization criteria for a cause-and-effect relationship (12) but go on to state that “Despite a lack of mechanism of action, the strong re-challenge data (9) suggest the drug effect may be significant.”

To understand whether there is a cause-and-effect relationship between erectile dysfunction drugs and NAION, one must consider basic scientific facts related to NAION as well as to the drugs.

BLOOD SUPPLY OF THE OPTIC NERVE HEAD

Studies on the blood supply of the optic nerve head (ONH) (13,14), as well as experimental (15), pathologic, and clinical findings, have all shown that NAION is caused by ischemia of the ONH (16). Therefore, the most important considerations in understanding the development of NAION are the factors that influence blood flow in the ONH. Evidence shows that blood flow is influenced by many factors, including systemic arterial blood pressure, endothelial-derived vasoactive agents, and autoregulation of blood flow in the ONH (17). Autoregulation is deranged by many systemic and local causes, including the aging process, arterial hypertension, diabetes mellitus, marked arterial hypotension from any cause, arteriosclerosis, atherosclerosis, hypercholesterolemia, vasospasm, and probably regional vascular endothelial disorders (17–20).
RISK FACTORS FOR NAION

My studies have shown that NAION is a multifactorial disease, with many risk factors playing a role in its development (21,22). They can be divided into predisposing and precipitating risk factors.

Predisposing Risk Factors

Predisposing risk factors are those that make a person susceptible to develop NAION but do not necessarily produce it. They may be systemic or local in the ONH. Systemic risk factors include arterial hypertension, arterial hypotension (particularly nocturnal), diabetes mellitus, hyperlipidemia, atherosclerosis, arteriosclerosis, migraine and other vasospastic disorders, defective cardiovascular auto-regulation, sleep apnea, hematologic disorders, and others (22). Local risk factors include increased intraocular pressure, marked optic disc edema from any cause, location of the watershed zone of the posterior ciliary arteries in relation to the optic disc, and vascular disorders in the nutrient vessels of the ONH (22). Pomeranz et al (5) concluded that “A small cup-to-disc ratio may be a risk factor for development of NAION in association with the use of sildenafil.” Our studies have shown that an absent or small cup is simply a secondary contributing factor, once the process of NAION has started, and not a primary factor (23).

Precipitating Risk Factors

In the presence of predisposing risk factors, precipitating risk factors act as the “last straw.” In a study of 925 episodes (involving 871 eyes) of NAION (24), 73.3% had a definite history of discovering the visual loss first upon awakening or at first opportunity to use vision critically after sleeping; in the remaining episodes, time of onset was generally uncertain. This shows that nocturnal arterial hypotension acted as the precipitating factor in the vast majority. Also, 24-hour ambulatory blood pressure monitoring studies (25,26) have shown a significant correlation between progressive visual loss in NAION and nocturnal arterial hypotension. Therefore, contrary to the prevalent misconception, NAION is largely a hypotensive disorder, not an embolic or thrombotic disorder. This is in sharp contrast to other strokes, which are primarily embolic or thrombotic phenomena.

Our 24-hour ambulatory blood pressure monitoring studies in over 700 patients so far have shown the following:

1. Taking blood pressure-lowering medication in the evening or at bedtime aggravates the physiological decrease of blood pressure during sleep, resulting in nocturnal arterial hypotension (26,27).
2. Daytime blood pressure often is no guide to the nighttime blood pressure or to the extent of decrease in blood pressure during sleep. We have not infrequently seen patients with ideal daytime blood pressure who developed a marked decrease during sleep without being on any treatment (22,26).
3. Patients with “white-coat hypertension” are often treated aggressively, resulting in marked nocturnal arterial hypotension, putting them at risk for developing NAION (25).
4. There is a significant correlation between progressive visual loss in NAION and nocturnal arterial hypotension (25,26).

ERECTILE DYSFUNCTION DRUGS AND NAION

In the light of this basic scientific information on NAION, let us evaluate the role of erectile dysfunction drugs in the development of NAION.

Cardiovascular Risk Factors Are Common in These Patients

Most reported cases are from middle-aged and elderly men. Arterial hypertension, diabetes mellitus, hyperlipidemia, and other systemic cardiovascular risk factors are common in this group. As discussed above, those factors predispose them to develop NAION.

NAION Has Occurred Shortly After Drug Use

In most of the reported cases of NAION after ingestion of sildenafil, the patient has detected visual loss upon awakening in the morning, as have most NAION patients (24).

Other Contributory Drugs Are Often Used

Patients with arterial hypertension and other cardiovascular disorders invariably take beta-blockers, angiotensin-converting enzyme-inhibitors, calcium channel blockers, or other drugs with arterial hypotensive effect. In their study on the combination of antihypertensive therapy with sildenafil or placebo, Mahmud et al (28) stated that “The extent of individual maximum reductions (in mm Hg) from baseline in systolic (24 ± 10 versus 6 ± 8; P < 0.05) and diastolic blood pressure (8 ± 5 versus 3 ± 2; P < 0.05) occurred on the sildenafil study day.” Patients with benign prostatic hypertrophy are often advised to take alpha adreno-receptor blocking agents at bedtime which can produce nocturnal arterial hypotension (26,27). Erectile dysfunction is one side effect of these and many other arterial hypotensive drugs.

Erectile Dysfunction Drugs Cause Systemic Hypotension

It is well established that sildenafil use is associated with a decrease in blood pressure (28–30). Our 24-hour ambulatory blood pressure monitoring studies (26,27,31)
have shown that arterial hypotensive medication taken in
the evening or bedtime aggravates the normal physiological
decrease of blood pressure during sleep, resulting in marked
nocturnal arterial hypotension. Erectile dysfunction drugs
are taken most often in the evening or before going to bed
so that their arterial hypotensive effect is likely to aggravate
physiologic nocturnal hypotension, especially if the patient
takes other drugs with hypotensive effects.

**Erectile Dysfunction Drugs Stimulate Release of Vasoconstrictors**

Phillips et al (32) showed that sildenafil causes an in-
crease in plasma norepinephrine levels by 31% ± 5% (P =
0.004) and concluded that sympathetic activation may have
implications for understanding cardiovascular events
associated with sildenafil use. It is well known that nor-
epinephrine is a potent vasoconstrictor. In malignant arterial
hypertension, ONH ischemia and NAION may be the result
of diffusion of vasoconstrictor agents from the peripapillary
choroid into the ONH (18). This phenomenon may be yet
another contributory factor in development of NAION after
sildenafil use.

**Stroke and NAION May Follow Rechallenge with Erectile Dysfunction Drugs**

Morgan et al (33) describe a patient who suffered a
transient ischemic attack followed by a stroke in the same
distribution six days later, with each event being associated
with sildenafil use. In another study (34), Humphrey
perimetry performed after ingestion of 200 mg sildenafil in
a healthy young woman showed bilateral superior and
inferonasal visual field depression. A critical review of all
the reported cases shows a close temporal relationship
between the ingestion of these drugs and the onset
of NAION.

This evidence indicates that a cause-and-effect re-
lation between the drugs and development of NAION is
likely. Skeptics may use the arguments that follow to
dispute this point.

**NAION Seems to Occur in Patients Using Erectile Dysfunction Drugs Who Have No Evident Systemic or Vascular Predisposing Risk Factors**

Having studied more than a thousand patients with
spontaneously-occurring NAION, I can confirm that many
patients seem perfectly healthy by the usual standards. But
there are serious limitations in our ability to detect NAION
risk factors. For example, a patient may be having marked
nocturnal arterial hypotension when the daytime blood
pressure is absolutely ideal. Whereas it is always assumed
that atherosclerosis is a disease of the elderly, atheroscle-
rotic plaques in the coronary arteries have been seen among
young (average age, 22 years), healthy American soldiers
killed in the Korean War (35). Also, in humans, we have no
means to determine the local risk factors in the ONH
mentioned above (17,36).

**Erectile Dysfunction Drugs Have Been Used for a Long Time before NAION Develops**

Whereas it is true that many cases of NAION have
occurred in patients who have been using erectile dys-
function drugs for a long time, it may be that a critical
decrease in blood pressure is required to produce the degree
of hypoperfusion of the ONH to cause NAION in sus-
ceptible persons. The requisite combination of factors to
cause threshold perfusion failure in the ONH may not be
present after every use of erectile dysfunction drugs. This is
well illustrated by the fact that patients suffer successive
attacks of NAION in the same eye (37) or the other eye (38)
days, months, or even years apart.

**Erectile Dysfunction Drugs Do Not Lower Perfusion of the Optic Nerve Head**

Pomeranz and Bhavsar (7) have stated that Grunwald
et al (39) found no significant change in the ONH blood
flow with sildenafil as compared with placebo use. How-
ever, Grunwald et al (39) measured ONH blood flow with
the laser Doppler flowmeter, a device that does not measure
ONH blood flow reliably (40). Results based on this
method may not be valid (41).

Despite these points, I believe that there is sufficient
evidence to support a cause-and-effect relationship between
the ingestion of erectile dysfunction drugs and the develop-
ment of NAION. Most probably, the incidence of NAION
after use of these drugs is much higher than is apparent
from the reports because patients are not always forthcom-
ing to physicians about their use of these drugs, owing to
embarrassment or their belief that this is not relevant
information. Given the information I have presented,
patients with cardiovascular risk factors, diabetes mellitus,
those who take arterial hypotensive drugs, and those who
have a history of previous NAION should be advised
against the use of erectile dysfunction drugs.

**REFERENCES**


Abstract: Four ophthalmic manifestations make up a substantial proportion of the indications for carotid endarterectomy (CE). They include transient monocular visual loss (TMVL), ocular ischemic syndrome (OIS), retinal artery occlusion (RAO), and asymptomatic Hollenhorst plaque. Critical review of the literature shows that the evidence to support the efficacy of CE in these four settings is tenuous.


Carotid endarterectomy (CE) is a widely performed operation in patients with critical stenosis of the cervical carotid artery (1–4). The evidence to support the efficacy of CE in prevention of stroke is based on several large collaborative trials (5,6). These trials have included patients whose manifestations are entirely ophthalmic, and it is estimated that these manifestations are currently the basis for up to 25% of transient ischemic attacks (7). A 2001 report (8) released evidence from one of the major CE clinical trials that suggests that CE is not effective in preventing stroke in most patients with transient monocular visual loss (TMVL). The evidence for the efficacy of CE in the three other ophthalmic manifestations (ocular ischemic syndrome [OIS], retinal artery occlusion [RAO], and asymptomatic Hollenhorst plaque) is also weak (Table 1).

TRANSIENT MONOCULAR VISUAL LOSS

The North American Symptomatic Carotid Endarterectomy trial (NASCET) (5) and the European Carotid Surgery Trial (ECST) (6) showed that CE was beneficial in reducing the risk of stroke in patients who had 70%–99% stenosis of the internal carotid artery noted within 180 days after hemispheric or monocular transient ischemic attack (TIA) or minor hemispheric stroke. In the original NASCET and ECST publications, the efficacy of CE applied to the patient group as a whole; the data for the 49% patients who had isolated monocular TIA (or TMVL) were not reported.

In 2001, Benavente et al (8) finally compared the NASCET stroke rate among patients who presented with TMVL to that of patients with 50%–99% carotid stenosis who presented with hemispheric TIA (HTIA). TMVL was the presenting symptom in 397 patients; HTIA was the presenting symptom in 829 patients. The 3-year risk of ipsilateral stroke among medically treated patients with TMVL was 10%, whereas in patients with HTIA, it was 20%. Thus, the non-surgically treated patients with TMVL were at substantially lower risk of hemispheric stroke than were those with HTIA.

Among the patients with TMVL, the degree of stenosis was, surprisingly, not a risk factor for stroke. Stroke occurred in 10.1% of patients with 70%–79% stenosis, in 9.8% of those with 50%–69% stenosis, and in 9.1% of those with total occlusion of the internal carotid artery. However, there were six risk factors for stroke in the TMVL group: 1) male, 2) age of 75 years or older, 3) history of HTIA or stroke, 4) history of intermittent claudication, 5) ipsilateral internal carotid artery stenosis of 80%–94%, and 6) absence of collateral vessels on angiography. Among medically treated patients with one of the above risk factors, the 3-year risk of ipsilateral stroke was 1.8% (low-risk group). For those patients with two risk factors, it increased to 12.3% (moderate-risk group), and among those with three or more risk factors, it reached 24.2% (high-risk group).

Among TMVL patients who underwent CE, the absolute reduction in the 3-year stroke risk was 2.2% in the low-risk group, 4.9% in the moderate-risk group, and 14.3% in the high-risk group. Thus, in the low-risk group, which comprised 80% of the TMVL patients, CE was harmful. In the moderate-risk group, CE was only mildly beneficial; in more than a 3-year period, 20 patients would have had to undergo CE to prevent one stroke. In the high-risk group, CE was more beneficial; even so, seven patients would have had to undergo CE to prevent one stroke.

Why should the stroke risk in patients with TMVL be so much lower than it is in patients with HTIA? One hypothesis is that it takes smaller emboli to impair vision than other brain functions, and such small emboli might be unlikely to cause future hemispheric stroke. A second hypothesis is that TMVL is caused by a mechanism other than embolism from the carotid artery (9). Regardless of the
explanation, the only reasonable interpretation of the recent NASCET data (8) is that CE should not be performed in patients with fewer than two of the above-mentioned risk factors and is of questionable benefit in those who have fewer than three risk factors.

**OCULAR ISCHEMIC SYNDROME**

OIS is characterized by rubeosis iridis, venous stasis retinopathy, narrowed retinal arteries, mid-peripheral retinal hemorrhages, posterior segment neovascularization, and increased intraocular pressure (10). The association of extracranial carotid artery occlusive disease with OIS has been well described (11). It is estimated that 5% of patients with marked carotid artery stenosis present with OIS (12). Is their visual prognosis and risk of stroke affected by CE?

Most reports involve single cases with poor documentation and short follow-up. There are only two published series. Rubin et al (13) reported 18 patients who underwent CE for OIS manifested by rubeosis iridis, venous stasis retinopathy, and increased intraocular pressure. In that series, 11 patients complained of intermittent or persistent loss of vision, 5 described pain in or around the eye, and 2 were asymptomatic. All patients had visual acuity measurements, slit lamp examination, ophthalmoscopy, ophthalmodynamometry, and photostress testing. Abnormalities on ophthalmoscopy were noted in 15 eyes. After CE, 14 patients described improvement in vision and in pericentral pain. Visual acuity improved in 6 patients and was unchanged in 11 patients. Ophthalmoscopic examination after surgery revealed improvement in ischemic findings in 14 eyes and total resolution in 4 eyes.

Sivalingam (14) found no benefit of CE in 52 patients who presented with OIS. In this group, 28% of the carotid arteries ipsilateral to the ischemic eyes were treated with CE. Only 7% of the eyes had improved visual acuity one year after surgery; 60% of the eyes actually had worse visual acuity at one year.

With so little published documentation, it seems that the verdict is still out on whether CE is beneficial in improving visual outcome and reducing stroke risk in patients who present with signs consistent with the OIS.

**RETINAL ARTERY OCCLUSION**

RAO is often presumed to result from extracranial carotid artery embolism, but other mechanisms may be causative, including orbital trauma, coagulopathies, migraine, use of oral contraceptives, and carotid angiography. In two large series of CE performed in patients with RAO (15,16), a relatively small proportion of patients had hemodynamically significant carotid stenosis. For example, among 34 patients with idiopathic RAO reported by Merchut et al (15), only four had ipsilateral internal carotid artery stenosis of 80% or more. Ipsilateral carotid artery stenosis of 60% or less was found in five (15%) patients, and entirely normal studies were found in five (15%) patients. Appen et al (16) reported occlusive disease of the ipsilateral internal carotid artery in 11% of 44 patients with central RAO.

There is only one adequately documented series that describes the results of CE in RAO patients (17). In this nonrandomized study of 23 patients, 16 underwent CE. None of the CE patients had a subsequent neurologic event during an average follow-up period of 18.7 months. Among these 16 operated patients, two had complete occlusion of the internal carotid artery, one had more than 90% stenosis, and 13 had less than 50% stenosis. Three of the seven patients (43%) in the non-surgical group had a stroke during

<table>
<thead>
<tr>
<th>Condition</th>
<th>Benefit of carotid endarterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient monocular visual loss</td>
<td>Only if three or more of the following features are present:</td>
</tr>
<tr>
<td></td>
<td>1) male</td>
</tr>
<tr>
<td></td>
<td>2) age of 75 years or older</td>
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<tr>
<td></td>
<td>3) history of HTIA or stroke</td>
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<tr>
<td></td>
<td>4) history of intermittent claudication</td>
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<td></td>
<td>5) ipsilateral internal carotid artery stenosis of 80%-94%</td>
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<td></td>
<td>6) absence of collateral vessels on cerebral angiography</td>
</tr>
<tr>
<td>Ocular ischemic syndrome</td>
<td>Uncertain because of insufficient evidence</td>
</tr>
<tr>
<td>Retinal artery occlusion</td>
<td>Uncertain because of insufficient evidence</td>
</tr>
<tr>
<td>Asymptomatic Hollenhorst plaque</td>
<td>Probably none</td>
</tr>
</tbody>
</table>

**TABLE 1. Indications for carotid endarterectomy in four ophthalmic conditions**

HTIA = hemispheric transient ischemic attack.
the mean follow-up period of 28.3 months. This difference was statistically significant, so the authors recommended CE in RAO patients who are found to have carotid artery stenosis, without specifying the degree of stenosis that would warrant CE.

**ASYMPTOMATIC HOLLENHORST PLAQUE**

Hollenhorst plaques, or intraluminal retinal cholesterol/fibrin deposits, are commonly found on routine ophthalmologic examinations of visually asymptomatic patients. Is CE beneficial in preventing stroke in patients who have asymptomatic Hollenhorst plaques? This issue may be approached first by considering the indications for CE in asymptomatic carotid artery stenosis without Hollenhorst plaques. The Asymptomatic Carotid Atherosclerosis Study (ACAS) (18) enrolled 1,662 patients with asymptomatic carotid artery stenosis of 60% or more discovered during evaluation for peripheral vascular surgery, contralateral CE, or a carotid bruit. Patients were randomized to conventional medical management (325 mg regular aspirin) or CE. The estimated 5-year ipsilateral stroke rate was 11% in the medically managed group and 5.1% in the CE group. The estimated 30-day morbidity and mortality of the ACAS patients, including complications of angiography, was 2.7%. Therefore, although the study concluded that CE decreases the risk of stroke in asymptomatic patients with more than 60% stenosis of the internal carotid artery, the benefit disappears if the perioperative morbidity and mortality rate exceeds 3% (18). Notably, the Carotid Artery Stenosis with Asymptomatic Narrowing Operation Versus Aspirin (CASANOVA) trial (19) did not show a benefit of CE over medical treatment of patients with asymptomatic carotid stenosis. In that study, the surgical complication rate was 11.4%, far exceeding a level that would provide benefit of CE in asymptomatic carotid stenosis. The Asymptomatic Carotid Surgery Trial (ACST) (20) enrolled 3,120 patients with at least 60% carotid artery narrowing but without neurologic symptoms during the six months before enrollment in the study. Patients were randomized to early CE (1,560 patients) or to deferred CE (1,560 patients). All patients were followed for at least five years with intent to follow the patients for ten years and received antihypertensive agents, antiplatelet agents, and lipid-lowering medication when indicated. Among those allocated to early CE, 50% had the procedure performed within one month of enrollment, 88% within one year, and 91% within five years. The remaining 8.2% did not have CE, although it had been planned for them. In the deferred CE group, 229 underwent CE, 6.9% within one year and 20.0% within five years. The remaining 73.9% of the patients in this group did not undergo CE. The 5-year estimated stroke risk was 6.4% in the early CE group and 11.8% in the delayed CE group. These results included a 3% perioperative morbidity and mortality risk. The probability of a stroke was not affected by the amount of carotid stenosis; the 5-year stroke risk was 2.1% in CE patients with less than 80% stenosis and 3.2% in CE patients with more than 80% stenosis. Thus, the results in ACST remarkably replicated those of the earlier ACAS trial. Although CE seemed to reduce the risk of stroke, the benefit was minimal.

Schwarcz et al (21) evaluated the role of CE in 64 patients with Hollenhorst plaques, most of whom were asymptomatic. Among 28 patients in whom CE was performed on the side of the Hollenhorst plaque, 24 were visually asymptomatic. No CE was performed on 39 patients, 37 of whom were visually asymptomatic. Patients were observed for 50 months with periodic ophthalmologic, neurologic, and noninvasive vascular examinations. The mean annual rate of stroke ipsilateral to asymptomatic Hollenhorst plaques was 2.4% in patients who underwent CE and 3.0% in those who did not undergo CE, a difference that was not statistically significant.

The authors concluded that in patients with asymptomatic Hollenhorst plaques, CE should not be recommended unless the patient develops hemispheric symptoms or signs referable to the appropriate carotid circulation and, even then, medical management is probably better.

**REFERENCES**


Carotid Endarterectomy for Ophthalmic Manifestations: What Do We Do?

David Nicolle, MD, and Vladimir Hachinski, MD

In the use of carotid endarterectomy (CE), the Department of Clinical Neurological Sciences in London, Ontario, follows the guidelines derived from the North American Symptomatic Carotid Endarterectomy Trial (1), which was organized at our institution.

In our hospital, three surgeons perform between 100 and 110 CEs and between 10 and 20 cervical carotid stents each year. Most patients are referred from the southwestern Ontario region. Our complication rate for CE is 1% for death and 1% for major stroke.

This is how we currently manage patients with the four major ophthalmic indications for CE:

1) Transient monocular visual loss (TMVL): These patients undergo carotid Doppler ultrasound and transesophageal echocardiography (TEE). TEE is preferred over transthoracic echocardiography because TEE allows a better look not only at the left atrium, but also the ascending aorta, which is often an unrecognized source of emboli. If the carotid ultrasound shows hemodynamically significant stenosis, the next step would be cerebral angiography. More recently, contrast-enhanced magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) have been used with increasing frequency. The reason for this shift is that MRA and CTA are less dangerous because they do not involve catheterization and are also cheaper and quicker.

If the echocardiogram test shows a plausible source of emboli, the patient would be anticoagulated with warfarin. Eighty-one milligrams of aspirin per day may be added if atherosclerotic carotid arteries were also found, although this increases the risk of bleeding and must be individualized.

If the internal carotid artery shows more than 70% stenosis, CE is offered to the patient. If a cardiac or aortic source has been found by echocardiography and the patient has been anticoagulated, the anticoagulation would be stopped to do the CE and then started up again after the surgery. Carotid stenting may be offered if there are significant medical problems precluding CE.

If there is 50%–70% stenosis of the internal carotid artery, CE is performed only in men who have also suffered one or more hemispheric transient ischemic attacks, particularly if the transient ocular ischemic attack has occurred within 48 hours. In the 50%–70% stenosis group, less benefit has been shown for women, and surgery is seldom recommended. If there is less than 50% internal carotid artery stenosis, we do not perform CE.

2) Central retinal artery occlusion (CRAO): This condition is also initially evaluated with carotid ultrasound and TEE, as well as a sedimentation rate (to exclude temporal arteritis). Management guidelines for CE are the same as for TMVL.

3) Asymptomatic Hollenhorst plaque (cholesterol retinal emboli): CE is not performed, irrespective of the degree of internal carotid artery stenosis. Such patients undergo TEE to exclude a cardiac or aortic source of emboli and a carotid ultrasound if the TEE is negative. We do not operate on these asymptomatic patients because the stroke rate is very low and there is no difference between medical treatment and CE.

4) Ocular ischemic syndrome (OIS): Patients with OIS typically have severe internal carotid artery stenosis or complete occlusion. Those with more than 70% stenosis are offered CE because it may help in stopping the progression of the ocular ischemia. CE is not offered for total carotid artery occlusion because the success rate of opening the artery in an occlusion is low and there is a high complication rate of stroke.

Acknowledgment

The authors gratefully acknowledge the help of Dr. Don Lee and Dr. Gary Ferguson.

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A 60-year-old man develops sudden complete transient loss of vision OD three days ago lasting 30 seconds. It occurred while he was reading. He has a history of medication-controlled hypertension and has smoked 1/2 pack of cigarettes daily for many decades. His medical history is otherwise unremarkable. General physical, ophthalmological, and neurological examinations are normal.

What is the probable cause of the deficit, and what is the next step in evaluation?

Louis R. Caplan, MD:

The most likely cause of his transient monocular visual loss (TMVL) is retinal ischemia (1–3). Occasionally, transient optic nerve ischemia can present similar symptoms (3). Most ocular ischemia is caused by embolism to the ophthalmic artery, and its branches that feed the retina and optic nerve. Sources of embolism to the eye include the heart, aorta, ipsilateral extracranial and siphon portions of the internal carotid artery, and the ophthalmic artery.

In this patient, a normal ophthalmologic examination excludes impending central retinal vein occlusion (4), optic disc drusen (5), and pre-retinal loops (6), which are occasional causes of ocular ischemia. There were no Hollenhorst plaques, white platelet-fibrin thrombi, or calcific emboli within the retinal arteries—clues to the origin of emboli. The risk factors in this patient make internal carotid artery (ICA) disease the most likely source of TMVL. Atheromatous disease of the aorta or heart is another important possibility. Patients with polycythemia and thrombocytosis can occasionally develop TMVL. Temporal arteritis is an infrequent cause.

I would begin by ordering a complete blood count and sedimentation rate, an electrocardiogram (EKG), a duplex ultrasound study of the neck arteries, and a transcranial Doppler (TCD) exploration of the cranial arteries. The duplex examination should detect significant ICA disease at the common carotid artery bifurcation. TCD can help detect disease of the carotid siphon proximal to the ophthalmic artery, disease of the ophthalmic artery itself, and help to quantify any reduction in blood flow related to ICA disease in the neck (7). If the duplex findings in the neck are equivocal, 20–30 minutes of TCD monitoring of the intracranial middle cerebral arteries (MCAs) might help identify the presence and source of emboli (8,9). If the source is the ipsilateral ICA, embolic signals would be detected only in the ipsilateral MCA; if the source is cardiac or aortic, emboli should be detected bilaterally. If a four-probe embolic detection system is available, the ICAs can also be probe sites. Emboli from the heart or aorta would first be detected in the ICA and shortly thereafter in the ipsilateral MCA. If the emboli arise from the ICA, no embolic signals would be heard in the neck.
I usually order a brain and head-and-neck vascular imaging study (computed tomography [CT]/CT angiography [CTA] or MRI/MR angiography [MRA]) along with the ultrasound. Some patients have had unexpected brain infarcts; their distribution can give a clue as to their cause. Brain infarction ipsilateral to ICA disease also tells of the biological activity of the lesion despite lack of symptoms (10,11). CTA and MRA examinations of the neck and head can show the presence, extent, and morphology of an ICA lesion in the neck and provide images of occlusive disease that might involve the pharyngeal portion of the ICA (such as fibromuscular dysplasia or dissection), the ICA siphon, and its ophthalmic artery branch.

An EKG should have detected atrial fibrillation and recent or past myocardial infarction. A transesophageal echocardiogram (TEE), which searches for embolic sources in the cardiac ventricles, atria, interatrial septum, cardiac valves, and aorta, might be indicated depending on the results of the blood tests, EKG, neck ultrasound, TCD, and brain and vascular imaging (12).

Norman R. Hertzer, MD:

Despite its unusually brief duration, this episode of TMVL almost certainly represents retinal microembolization, which, in this case, probably was related to platelet thrombi given the transitory nature of the event and the absence of any atheromatous debris observed in the retina. Until proven otherwise, atherosclerotic stenosis or ulceration in the ipsilateral carotid bifurcation represents the most likely embolic source in this patient, especially considering his long history of tobacco use. If cervical carotid disease can be excluded by appropriate studies, however, then cardio-embolic and other less common etiologies would have to be investigated (13). In an effort to prevent any further micro-embolic events while the diagnosis is being established, the patient should immediately be instructed to begin taking aspirin at least 81 mg/day (14).

The next step in the evaluation would be a carotid duplex scan, preferably at a facility that has been certified for accuracy by the Intersocietal Commission for the Accreditation of Vascular Laboratories (www.iacvl.org). Provided high-grade (70%-99% or 80%-99%) extracranial carotid stenosis is identified on the basis of reliable duplex scanning, carotid endarterectomy (CE) could legitimately be recommended without the small additional risk of a confirmatory arteriogram (15). But if the duplex scan reveals only mild to moderate cervical carotid disease, MRA or even catheter arteriography may be required to exclude non-stenotic plaque ulceration, aortic arch lesions, or intracranial carotid siphon disease proximal to the origin of the ophthalmic artery. An echocardiogram might be indicated if the underlying etiology still remains in doubt.

The patient undergoes a duplex cervical carotid ultrasound that reveals 80% cross sectional stenosis on the right and 50% on the left. A brain MRI is negative. What do you advise as the next step?

Louis R. Caplan, MD:

I would first review the results with the patient, indicating that he has significant carotid artery disease and is at risk for stroke. I would explain that the alternatives are maximal medical therapy, CE, or carotid angioplasty/stenting. Maximal medical therapy, which consists of an antiplatelet agent, a statin in the appropriate dose, and an ACE inhibitor or ACE receptor blocker, would be prescribed. Although the risk of stroke after a retinal transient ischemic attack (TIA) is about one third the risk of stroke after a hemispheric TIA (16), it is likely to be more than 10% during the ensuing year or two (16). If he opted for medical treatment and was to have a hemispheric TIA or minor stroke, then the risk of major stroke would increase considerably, and aggressive therapy would be mandated.

If medical treatment has not been optimal, consideration should be given to adding a statin or increasing the dose of a statin if one is already being used. Studies have shown that large doses of statins can reduce plaques or at least stabilize them and reduce the frequency of stroke (17–20). ACE inhibitors and ACE receptor blockers have also been shown to have salutary effects on the endothelium and could be prescribed (21,22). Some antiplatelet agents, especially an aspirin-dipyridamole combination or cilostazol, have effects on platelets and vascular endothelium and may be more protective than aspirin alone or clopidogrel. These medical prescriptions can be given while further investigations are performed and while the patient is deciding on a preferred strategy of treatment.

The nature of the carotid plaque might influence prognosis and treatment. The main features are plaque echogenicity, regularity, homogeneity, location, and the thinness of the fibrous cap overlying the plaque (23–25). Hypoechoic plaques contain more macrophages and lipid materials and are more likely to become symptomatic (and to be reducible by statins). Hyperechoic material indicates calcium and stability. Heterogeneity and irregularity of the surface, especially with ulceration, carry a worse prognosis for symptom development. These features can now be detected by high-quality B-mode ultrasound and, in some
centers, by modern CT and MRI imaging of plaques using cross-sectional views of the artery.

Brain imaging is also useful. The presence of brain infarcts on CT or MRI attributable to the stenotic artery gives evidence of biological activity of the carotid disease despite the absence of hemispheric symptoms and increases the risk of stroke (10). Embolic monitoring also provides prognostic data. The number and frequency of microemboli (high-intensity transient signals on TCD) and their response to medical treatment is predictive of symptom development (26–28).

If the patient makes up his mind to undergo CE or stenting, I would refer him to the appropriate specialist. If he is opposed to a procedure, I would maximize medical treatment and instruct him about hemispheric attacks. If he is uncertain and believes that more data would help him decide, I would schedule further investigations such as cranial MRI, high-quality duplex ultrasound, and TCD of the intracranial arteries, along with embolic monitoring.

Norman R. Hertzer, MD:

For over a decade, the importance of identifying symptomatic carotid disease primarily has been predicated on the conclusions of the North American Symptomatic Carotid Endarterectomy Trial (NASCET). In this prospective, multicenter clinical trial, patients having a recent history of TMVL, transient hemispheric ischemia, or non-disabling stroke were randomized to receive CE plus “optimal” medical management (predominantly antiplatelet therapy) or medical management alone for either 50%–69% or 70%–99% carotid stenosis documented on the appropriate side of the neck by arteriography.

The initial NASCET results were reported in 1991 for 70%–99% stenosis (29) and demonstrated that CE significantly reduced the 2-year ipsilateral stroke rate as compared with medical management alone (9% versus 26%; \( P < 0.001 \)). Interestingly, subset analysis later revealed that patients in the medical cohort who originally presented with transient hemispheric TIA or stroke had a higher 2-year stroke rate than did patients who presented with TMVL (43.5% ± 6.7% versus 16.6% ± 5.6%; \( P = 0.002 \)), representing a relative risk ratio of 3.23 (95% confidence interval, 1.47–7.12) (16).

It took substantially longer for the NASCET trialists to reach conclusions regarding the efficacy of CE in symptomatic patients who had only 50%–69% carotid stenosis. Their 1998 report (30) showed that, whereas still statistically significant, the benefit of surgical treatment was much less convincing. The 5-year ipsilateral stroke rate for CE in these patients was 15.7% versus 22.2% in medically treated patients (\( P = 0.045 \)). CE provided no advantage in comparison to medical management for an exceedingly small group of only 36 patients who were randomized because of TMVL or retinal stroke.

Provided the duplex scan was performed in a reliable noninvasive vascular laboratory, I would recommend right CE by a qualified surgeon or participation in one of the current randomized trials comparing CE to percutaneous transluminal angioplasty (PTA) and stenting with the use of a cerebral protection device. The choice between these two options would depend in part on their availability at the center where he receives his care. I should also add that obtaining an MRI brain scan seems to have been an unnecessary extravagance in our patient, especially after only a single 30-second episode of TMVL. The chance that such a study would have revealed any useful information seems remote.

In 2001, Benavente et al (31) finally reported the outcomes of the subgroup of TMVL patients from the NASCET trial who were randomized to CE versus best medical treatment. As you recall, they found that a meaningful benefit of CE was restricted to those who had at least three of the following characteristics: age >75 years, male, history of hemispheric TIA or stroke, history of intermittent calf claudication, ipsilateral internal carotid stenosis >80%, or no collaterals on angiography. Our patient meets only two of these criteria. Is CE indicated?

Louis R. Caplan, MD:

The cited NASCET data (31) must be put in the perspective of the study. The analysis was retrospective. It considered effectiveness as reducing strokes (not just those related to the ipsilateral carotid artery). This means that factors related to strokes and vascular disease in general, such as hypertension, diabetes, hyperlipidemia, and smoking, were heavily weighted. The data analyses used indirect risk factors (age, sex, and claudication) as surrogates for estimating the seriousness of vascular disease. The percentage reduction of luminal size on catheter cerebral angiograms and the presence of collateral circulation were the main direct measures of the nature and severity of the carotid artery disease. The details of the composition and morphology of the stenosing plaques, as shown by high-quality ultrasound, were not included.
Several factors were not included or sufficiently emphasized, as is true in many large trials that must lump disparate patients. For example, the presence of brain infarcts in the territory of the stenosed artery and other medical therapies. Moreover, since the NASCET study was planned, advances in technology and treatment have occurred. There are new drugs and information about effective dosages of statins, ACE inhibitors, ACE receptor blockers, and non-aspirin platelet inhibitors, plaque morphology, as studied by modern ultrasound, the importance of brain infarcts seen on MRI, the ability to detect emboli by TCD, and the availability of carotid angioplasty/stenting.

Norman R. Hertzer, MD:

So many subset analyses from the NASCET have been published since the initial disclosures from this trial in 1991 that it has become increasingly difficult to keep track of all of them. Now that I have read the article by Benavente et al (31), I find that its data regarding the treatment of TMVL are based on 107 patients having none of the five stated risk factors, 150 patients having two of the risk factors, and 103 patients having three or more of the risk factors. These sample sizes apparently do not detract from the statistical validity of the conclusions, but they do parse the total NASCET population (n = 2,885) into some pretty small pieces. I personally would be very uncomfortable using this information to withhold CE from a symptomatic patient who has 80%-99% carotid stenosis merely because he is only 60 years old and does not claudicate.

Furthermore, it seems hard to know how the NASCET proportional hazards model applies to our patient because he has not yet had an arteriogram to demonstrate the presence or absence of collateral circulation distal to his high-grade cervical carotid lesion. An arteriogram presumably would have to be done in order to determine where he fits into the NASCET analysis, but findings from the Asymptomatic Carotid Atherosclerosis Study (ACAS) indicate that an arteriogram also would add a small but measurable risk to his management (32). Five (26%) of the 19 strokes or deaths contributing to the combined stroke and mortality rate of 2.3% in the surgical cohort of the ACAS were directly related to the preoperative arteriogram, an observation that undoubtedly has influenced a growing reliance on non-invasive testing alone in the selection of patients for CE. At the Massachusetts General Hospital, for example, only 10% of patients underwent preoperative arteriography before CE in 1998–1999 compared with 87% in 1989–1990 (33).

As a practical matter, two other large randomized trials—the ACAS and the more recent Asymptomatic Carotid Surgery Trial—have shown that our patient already has carotid stenosis of sufficient severity to justify prophylactic CE even if he had no symptoms whatsoever (32,34). For all of these reasons, I believe that he is an appropriate candidate for CE despite the fact that he has only two of the NASCET risk factors described by Benavente et al (31).

Of the two options, CE and angioplasty/stenting, which would you choose for this patient, or for others?

Louis R. Caplan, MD:

I would place some weight on the findings from high quality ultrasound and vascular imaging. Since the NASCET study, there have been a number of studies of the risks and benefits of angioplasty/stenting with and without protective devices (35–37). In a high carotid bifurcation or very long smooth plaque, stenting is likely better. In a very focal ulcerated lesion, surgery is likely better. If there is a tandem lesion distal to the bifurcation, then angioplasty/stenting might treat both lesions. The availability, experience, and complication rates of the surgeons and interventionalists are also important in deciding which treatment is preferable.

I would discuss the options with the patient, attempting to share the risks and benefits of each approach in his individual case and in relation to the individuals available to provide the treatments. All things being equal, I usually favor stenting or entering the patient into a randomized trial that compares stenting with surgery (38).

Norman R. Hertzer, MD:

First let me give a brief overview of catheter-based intervention for carotid bifurcation disease. Isolated case reports and experience with small series of patients suggested nearly two decades ago that angioplasty of the carotid artery might prove to be an appropriate alternative to traditional surgical treatment for high internal carotid lesions near the skull base, recurrent stenosis after previous CE, or a history of cervical irradiation (39).

Intraluminal stenting was introduced in the early 1990s to reduce the incidence of peri-procedural embolic events and recurrent stenosis that were associated with angioplasty alone, and over-the-wire cerebral protection devices were later developed in a further attempt to prevent strokes caused by atheromatous emboli dislodged during stent deployment. These refinements have widened the indications for catheter-based intervention, but as so often occurs with rapidly advancing technology, they also have turned outcome assessment into a moving target.
The elusive nature of this target can be illustrated by two relatively recent examples involving symptomatic patients. In 2000, Golledge et al (40) conducted a meta-analysis of 33 single-center studies that had been reported from 1990 through 1999 and calculated that the risks for any related stroke (7.1% versus 3.3%; \( P < 0.001 \)) or stroke or death (7.8% versus 4.0%; \( P < 0.001 \)) were significantly higher for angioplasty than for CE. In 2001, the results of a multicenter, prospective randomized trial (CAVATAS) conducted in Europe from 1992 to 1997 indicated that, whereas the 30-day combined stroke and mortality rates (CSM) of angioplasty and CE were uniformly poor (10% versus 9.9%), the 1-year incidence of recurrent 70% stenosis was significantly higher (14% versus 4.0%, \( P < 0.001 \)) for angioplasty (41). However, the conclusions of both of these investigations became obsolete nearly as soon as they were published for two reasons: 1) stenting had been done in only 44% of the angioplasty cases reviewed in the meta-analysis and in just 26% of the angioplasty cohort of the CAVATAS; and 2) cerebral protection devices were not yet available during either of the two study periods. Therefore, the evidence base for contemporary angioplasty/stenting with intra-procedural cerebral protection is limited to the past five years and still is evolving.

Two industry-funded trials now have shown outcomes for angioplasty/stenting with cerebral protection that are equivalent to CE in a mix of symptomatic and asymptomatic patients drawn from the United States. The CARESS study (Boston Scientific, Natick, MA; Medtronic AVE, Santa Rosa CA) is a Phase I clinical trial in which 397 typical patients were treated at 14 sites by angioplasty/stenting (n = 143) or CE (n = 254) (42). In that study, there were no significant differences in the 30-day CSM (2.1% versus 2.4%) or the CSM-plus-myocardial infarction (MI) rates (2.1% versus 3.1%). The other study is the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial (Cordis Corporation, Warren, NJ), in which 334 patients with medical comorbidities or anatomic features considered unfavorable for CE were randomized to angioplasty/stenting (n = 167) or CE (n = 167) at 29 participating centers (35). Using conventional end points consisting of the 30-day CSM plus ipsilateral stroke or death within 1 year, the SAPPHIRE trial had equivalent outcomes for angioplasty/stenting and CE (5.5% versus 8.4%; \( P = 0.36 \)). When increased peri-procedural cardiac enzyme levels also were considered, the CSM/MI plus 1-year event rates were lower for angioplasty/stenting than for CE (12% versus 20%; \( P = 0.05 \)).

The ongoing Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is a multicenter, prospective, randomized investigation that is supported by the National Institutes of Health with plans to recruit 1,200 to 1,600 symptomatic patients (43). No outcome data have been disclosed for approximately 650 randomizations, but information has been reported for 749 non-randomized patients who were treated with angioplasty/stenting with adjunctive cerebral protection during a lead-in phase used for credentialing catheter-based interventionalists at 51 sites (44). These results substantiate that the CSM for angioplasty/stenting is correlated with advancing age, ranging from 1.4% in 349 patients aged less than 70 years to 7.0% in 400 patients aged 70 years or older (\( P = 0.0006 \)). Others (45) have made similar observations regarding age and the early risk of angioplasty/stenting, despite the use of anti-embolic devices.

Now, which option would I choose for this patient? He does not represent a predictable early risk for either approach at only 60 years of age, and therefore, he should be given the opportunity to enroll in the CREST if a trial center is nearby. If not, his anticipated life expectancy becomes a consideration with respect to the risk for recurrent stenosis, which may be greater for angioplasty/stenting although this has not been rigorously verified for contemporary angioplasty/stenting techniques. In the absence of further data, I favor CE with carotid patching on the basis of my own experience. But the key point is: what are the comparative results of CE and angioplasty/stenting at the hospital where the patient will be treated? A decision concerning management options cannot be made objectively without this information.

Would your management differ if, instead of transient visual loss, this patient had presented with acute persistent unilateral visual loss owing to a central retinal artery occlusion (CRAO)? Would management differ if the patient had presented without visual symptoms but had been found to have a Hollenhorst plaque in one eye?

Louis R. Caplan, MD:

My suggestions for management would not be different had the patient presented with a CRAO. If he was asymptomatic and had a Hollenhorst plaque discovered incidentally, I would be heavily guided by the nature and extent of the carotid artery lesion. I would also lean more toward surgery if brain imaging disclosed a brain infarct in the carotid artery territory.
Norman R. Hertzer, MD:

None of the prospectively randomized trials of CE or angioplasty/stenting has generated data specifically concerning either CRAO or incidental Hollenhorst plaques, but independent case series suggest that these findings are much less likely than TMVL to be associated with serious underlying carotid stenosis. For example, three studies (46–48) have collectively reported at least 60% ipsilateral carotid stenosis by duplex scanning in 31 (37%) of 84 patients with TMVL, compared to just seven (11%) of 63 patients with Hollenhorst plaques and two (7.4%) of 27 patients with CRAO.

The observation that CRAO is a poor predictor of carotid artery disease is not surprising because it often is merely an ophthalmic manifestation of systemic illness, such as uncontrolled diabetes, arteritis, or a variety of coagulation disorders (49). For this reason, medical consultation probably should be obtained as one of the first steps in the evaluation of CRAO. If another plausible etiology is discovered, investigation of the carotid arteries may not be required provided, of course, that the onset of sudden monocular blindness had not been preceded by earlier episodes of classic TMVL in the same eye. With a history of previous TMVL, one might be more likely to suspect ipsilateral carotid emboli and proceed with a duplex scan.

Asymptomatic Hollenhorst plaques can originate from the heart or the aortic arch as well as from the carotid bifurcation, in which case additional retinal emboli and/or neurologic events may still occur even if CE already has been performed for what was thought to be the responsible lesion (50). This emphasizes the importance of a thorough ophthalmologic evaluation, because the presence of bilateral retinal atheroemboli would clearly imply that they share a common proximal source in the chest. Another dilemma in the management of Hollenhorst plaques is the fact that they may persist for as long as three years (51). Therefore, unless serial ophthalmologic examinations have documented that a Hollenhorst plaque is recent, it could have originated in an atheromatous ulcer in the ipsilateral carotid artery or elsewhere that has healed and is no longer a threat for further embolization.

Despite all of these uncertainties, a unilateral Hollenhorst plaque remains an appropriate indication for carotid duplex scanning if only because one does not want to overlook an easily accessible lesion for which anti-platelet therapy alone would offer no guarantee against future atheroembolic complications. It seems prudent, however, to limit CE or angioplasty/stenting strictly to patients who, like our own, have such severe carotid stenosis that they would be candidates for carotid intervention anyway.

If you were this patient, with the same scenario, what would you wish to have done?

Louis R. Caplan, MD:

Stenting with a competent experienced interventionalist using a protective device.

Norman R. Hertzer, MD:

I would first seek out a qualified surgeon, preferably one who holds the Certificate of Special or Added Qualifications in Vascular Surgery issued by the American Board of Surgery and who practices in a hospital at which the outcome of CE is continuously audited for quality assessment. I would then opt for CE with a patch because so many randomized and non-randomized studies now have shown that patching reduces the risks for postoperative death, postoperative stroke, late stroke, recurrent stenosis, and re-operations as compared with primary arteriotomy closure. In general, CE/patching is associated with a CSM less than 2%, a 5% incidence of recurrent stenosis, and a re-intervention rate of 3% or less (33, 52–56).

It may be that angioplasty/stenting will someday match these results and, at certain centers of excellence, perhaps it already does. At the present time, however, the technology of catheter-based carotid intervention and the learning curve of its practitioners are in their maturation phases. For this reason, I believe that CE with patching currently represents the best available approach throughout the countless communities, large and small, where most patients receive their care.

Rebuttals

Louis R. Caplan, MD:

It comes as no surprise that Dr. Hertzer, a renowned vascular surgeon, would choose vascular surgery over angioplasty/stenting. We tend to choose the more familiar over the less familiar. No doubt Dr. Hertzer would have access to a very capable, experienced vascular surgeon with a superb track record for CE, a luxury our patient may not have.
Dr. Hertzer's discussion and some of the queries emphasize trial data. Caring for individual patients is different from trials. The CREST and other trials pit CE against angioplasty/stenting with the naive idea that one approach is always superior to the other. Actually, one approach may be better for some lesions and some patients with coexisting conditions and risks. The location, content, extent, and morphology of the occlusive plaque are important determinants for the choice of treatments. The carotid artery investigations reported on this patient do not sufficiently detail this information. Also, trials assume equipoise between the surgeon and the interventionalist. As Dr. Hertzer notes, this is not always the case at the institution where the patient will be treated and heavily influences selection of strategy.

Most important, and again not included in trials, is the preference of the patient and the referring physician. General anesthesia poses a very definite risk and many doctors and patients would avoid it. CE is customarily performed under general anesthesia; angioplasty/stenting is not. Patients live in different socioeconomic-psychological milieus. Given the same information, they make different decisions. Some find the knowledge of a severe carotid lesion very difficult to live with. Told that they are at imminent risk of having a disabling stroke, they feel that a sword (the stenotic artery) is hovering over them. Some will gamble on removal of the sword. Others fear the knife and opt for no incision and remaining awake. Still others have heard of risk to their health from these interventions and will not let knowledge of their carotid artery disease interfere with their lives; they are content to pursue medical therapy and clinical monitoring. They may have decided that a stroke during surgery or stenting would affect them now, whereas the risk of stroke without aggressive intervention is spaced over the years ahead.

Patients should be provided with information and the pros and cons of each alternative. Doctors should convey their own advice and opinion, but ultimately, the patient has the right to choose. Trial data that average out results may not heavily influence some individuals.

Norman R. Hertzer, MD:

Aside from our personal preferences for CE or percutaneous angioplasty/stenting, the main areas in which I disagree with Dr. Caplan regarding the management of this patient involve the extent of his initial work-up and his willingness to continue medical management even after severe carotid stenosis has been documented by noninvasive imaging.

Dr. Caplan apparently would obtain a lot more tests than I feel are necessary for the evaluation of an otherwise healthy 60-year-old smoker who has had a single brief episode of TMVL. It would not cross my mind to order a sedimentation rate, a TCD examination, a head-and-neck CT/CTA, or an MRI/MRA for this patient before the duplex scan had even been performed. Once a reliable duplex scan has shown 80%-99% stenosis in the ipsilateral carotid bifurcation, the cost effectiveness of the other studies becomes very questionable. I believe they should be reserved for patients who have less than severe carotid stenosis by duplex scanning or some other specific reason for additional testing.

Dr. Caplan considers "maximal medical therapy" to be a reasonable alternative to CE or angioplasty/stenting in this patient. He then states that "if medical treatment has not been optimal" (that more symptoms have occurred), "consideration should be given to adding a statin" or some other refinements in medical management "while further investigations are performed and while the patient is deciding on a preferred strategy of treatment." Assuming for a moment that this patient, like most others, is content to follow whatever evidence-based advice is given to him, I think this is all a waste of time and merely places the patient at risk to have the stroke for which his TMVL was a warning event. His original symptom and the severity of his carotid stenosis already satisfy the criteria for intervention that have been established by several major randomized trials (NASCET (29), ACAS (32), and ACST (34)) comparing CE to best medical management. In my opinion, the patient should get on with it.

Editor's Summary

These two eminent physicians—a neurologist specializing in stroke and an experienced vascular surgeon—appear to agree on one fundamental point: that under the right circumstances, CE or angioplasty/stenting is indicated in this typical case of TMVL. They differ in other critical aspects.

Both experts accept the idea that surgical opening of the ipsilateral cervical carotid artery will improve the patient’s welfare. Dr. Caplan, the neurologist, cites the 1995 report (16) in which follow-up data from the NASCET study showed that patients with TMVL had a 16.6% 2-year risk of ipsilateral hemispheric stroke if they were managed medically. But he does not mention that not one of the TMVL patients in this study had a major stroke in the follow-up period! When confronted with the evidence from the 2001 NASCET report by Benavente et al (31) suggesting
that this patient would probably not meet criteria for
definite benefit of CE, Dr. Caplan points out that the study
does not incorporate the new and improved methods of
predicting stroke risk from carotid artery disease.

Dr. Hertzer, the surgeon, acknowledges the better outcome
of medically treated TMVL patients with high-grade
carotid stenosis. But to perform this analysis, he believes
that the NASCET cohort was excessively “parsed.” As
a result, he “would be very uncomfortable using this
information to withhold endarterectomy.”

After agreeing on that fundamental issue, the experts
diverge. Given the finding of hemodynamically significant
ipsilateral carotid stenosis, Dr. Caplan does not want to
make a recommendation until he knows more about the
patient’s medical risk factors and how they are being managed, the nature of the arterial lesion, heart, intracranial
circulation, and brain parenchyma. In asking for this information, he seems to be saying that: 1) he is not utterly
convinced that the impressive carotid stenosis is the cause of the TMVL; 2) he wants to fractionate the risk of stroke
better; and 3) he needs to know if there is room to improve medical management. Dr. Hertzer, on the other hand, says
that if you find convincing carotid stenosis with ultrasound, CE and angioplasty, Dr. Hertzer points out that the risk of
complication rates of the surgeons and interventionists.

In considering other ophthalmic indications for carotid intervention, the debaters also seem to differ. Dr. Caplan approaches a patient with new CRAO exactly as he
does a patient with new TMVL. Dr. Hertzer points out that
data show that CRAO patients are much less likely to have
high-grade ipsilateral carotid stenosis than are TMVL pa-
tients, but he would still recommend a carotid procedure if

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Cerebral Perfusion Imaging

Ellen G. Hoeffner, MD

**Abstract:** There are multiple imaging techniques available to assess cerebral perfusion, including positron emission tomography (PET), xenon computed tomography (XeCT), single photon emission computed tomography (SPECT), perfusion-weighted MRI (PWI), and perfusion computed tomography (PCT). Current interest has focused mainly on their use in the setting of acute brain ischemia. Perfusion imaging may be able to distinguish infarcted from salvageable ischemic tissue as a guide to treatment. Perfusion techniques may also be helpful in cases of chronic ischemia, post-subarachnoid hemorrhage vasospasm, trauma, and contemplated therapeutic carotid artery occlusion.


A variety of imaging techniques have been available to assess cerebral perfusion since the 1970s, beginning with positron emission tomography (PET) and xenon computed tomography (XeCT). Over the next two decades, single photon emission computed tomography (SPECT), perfusion-weighted MRI (PWI), and perfusion CT (PCT) were introduced into the armamentarium of perfusion imaging techniques (1). These techniques have been used to evaluate a variety of disease states, including acute and chronic ischemia, ischemia from post-subarachnoid hemorrhage (SAH) vasospasm, head trauma, and in the assessment of patients requiring therapeutic carotid occlusion (1,2). The advent of thrombolytic therapy to treat acute stroke has intensified the interest in perfusion imaging techniques in an attempt to distinguish already infarcted tissue from ischemic but potentially salvageable tissue (the ischemic penumbra) (3–5). Such imaging may allow for better selection of patients for thrombolytic therapy with the hope of improved outcomes and fewer complications. It may also allow expansion of the current therapeutic window of 3 hours for IV and 6 hours for intra-arterial tissue plasminogen activator (t-PA) (1). This article will review the currently available perfusion imaging techniques with an emphasis on PWI and PCT, the techniques most often used in current clinical practice (Table 1).

**DYNAMIC PERFUSION CT**

Dynamic PCT studies are obtained by monitoring the first pass of an iodinated contrast agent through the cerebral vasculature (4,6). Changes in tissue attenuation that occur in the brain after the contrast injection are measured (1,4,6). Post-processing of the PCT data allows the generation of color-coded maps of various perfusion parameters, including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and the time-to-peak (TTP), the time from the start of contrast agent injection to the time of maximum enhancement (1,2,7,8). The maps generated depend on the algorithm used in the processing of the perfusion CT data (4,6).

Recent studies have indicated that PCT may be able to distinguish reversible from non-reversible ischemia by assessing quantitative perfusion parameter values or generating maps of penumbra and infarct core using the quantitative data and special software (9,10). The latter method assumes that as CBF decreases, areas of reversible ischemia will have normal to increased CBV because of autoregulatory vasodilatation, whereas areas of irreversible infarction will have decreased CBV. Thus, low CBV areas may be comparable to restricted diffusion areas on diffusion-weighted images obtained by MRI (1,10). Results of initial studies attempting to define quantitative thresholds for areas of reversible ischemia and irreversible infarction indicate values similar to those obtained with other perfusion imaging modalities such as PET and XeCT (11,12) (Fig. 1). However, no studies have been performed assessing the ability of PCT to guide thrombolytic therapy or predict the risk of hemorrhage after thrombolysis (1).

Use of PCT in other clinical settings has been limited. It has been used in conjunction with an acetazolamide challenge to assess cerebrovascular reserve in patients with chronic oligemia (13,14). In many patients with carotid steno-occlusive disease, collateral circulation can maintain normal cerebral perfusion pressure and blood flow (15). If perfusion pressure is not maintained, cerebral autoregulatory vasodilation occurs to maintain near normal CBF with
a resultant increase in CBV (15). Paired CBF measurements before and after a vasodilatory stimulus, such as acetazolamide, can provide information about the presence of autoregulatory vasodilation and impaired reserve vasodilatory capacity. Acetazolamide normally causes vasodilation and an increase in CBF by at least 25% (16). But vascular territories under hemodynamic stress are already maximally vasodilated and cannot respond further to acetazolamide (15). CBF values in these regions will not increase appropriately. There may even be a decrease in CBF in the affected territory after acetazolamide injection as vasodilation in other well-perfused brain territories diverts blood away from fully vasodilated, poorly perfused regions (17). Improvement in PCT parameters after stenting or bypass has

### TABLE 1. Overview of perfusion imaging techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Perfusion parameters measured</th>
<th>Other imaging obtained</th>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>CT perfusion</td>
<td>CBF, CBV, MTT, TTP</td>
<td>NCCT, CTA</td>
<td>Fast (&lt;1 min of scanning time)</td>
<td>Accuracy and reproducibility of quantitative results not fully validated</td>
</tr>
<tr>
<td>MR perfusion</td>
<td>CBF, CBV, MTT, TTP</td>
<td>DWI, Routine MR images, MRA</td>
<td>Image nearly entire brain</td>
<td>Longer scanning time (15–20 min for PWI, more for additional sequences)</td>
</tr>
<tr>
<td>PET</td>
<td>CBF, CBV</td>
<td>OEF, CMRO₂</td>
<td>Well validated technique (“gold standard”)</td>
<td>Complex imaging technique with limited availability</td>
</tr>
<tr>
<td>SPECT</td>
<td>CBF</td>
<td>None</td>
<td>Relatively easy to perform</td>
<td>Limited availability</td>
</tr>
<tr>
<td>XeCT</td>
<td>CBF</td>
<td>NCCT</td>
<td>Quantitative and standardized</td>
<td>Limited availability</td>
</tr>
</tbody>
</table>

**CBF**, cerebral blood flow; **CBV**, cerebral blood volume; **CMRO₂**, cerebral metabolic rate for oxygen; **CT**, computed tomography; **CTA**, CT angiography; **DWI**, diffusion weighted imaging; **FDA**, Food and Drug Administration; **MR**, magnetic resonance; **MRA**, MR angiography; **MTT**, mean transit time; **NCCT**, non-contrast head CT; **OEF**, oxygen extraction fraction; **PET**, positron emission tomography; **PWI**, perfusion-weighted imaging; **SPECT**, single photon emission computed tomography; **TTP**, time to peak; **XeCT**, Xenon computed tomography.
been demonstrated in case reports (13,14), but there are no data on whether PCT can predict which patients are at higher risk of stroke or will benefit from revascularization. Studies of the use of PCT in patients with vasospasm after SAH and those undergoing carotid balloon test occlusion (BTO) are in preliminary stages (18,19) (Fig. 2). The high injection rates require the use of a large-bore IV catheter, which may cause patient discomfort.

PCT is a rapid technique requiring approximately 1 minute of scanning time and several minutes to obtain post-processed perfusion maps. It can potentially be widely available, requiring only a helical CT scanner and appropriate software (1,2). Other CT examinations, such as a non-contrast CT scan and CT angiography (CTA), can be obtained in the same setting. However, there are significant concerns regarding the accuracy and reproducibility of the quantitative values obtained with this technique (1). For example, only a limited area of the brain can be imaged with this technique, typically a 10 to 30 mm thick section, usually at the level of the basal ganglia, which limits visualization to portions of the anterior, middle, and posterior cerebral artery territories (1,2,8). PCT may be contraindicated in patients with contrast allergies or renal failure; the high injection rates require the use of a large-bore IV catheter, which may cause patient discomfort.

PERFUSION-WEIGHTED MRI

The most commonly used MR perfusion technique, is dynamic susceptibility contrast (DSC) imaging. It is similar to PCT in that a contrast agent (a gadolinium chelate) is injected intravenously that causes changes in the MR signal as the agent passes through the vasculature. The change in signal intensity is then measured and perfusion maps are generated, most commonly CBF, CBV, TTP, or MTT.

FIG. 1. CT perfusion imaging of acute stroke. (A) Axial CBF map shows decreased CBF (arrows) in the right occipital lobe, a finding that does not definitely differentiate reversible ischemia from infarct. (B) MTT is prolonged on the axial MTT map (arrows), consistent with findings on CBF map (A). (C) CBV is decreased (arrows) on axial CBV map, confirming that this area is infarcted. (D) Follow-up axial CT shows an infarct (arrows) in right posterior cerebral artery (PCA) territory.

FIG. 2. CT perfusion imaging of an acute stroke related to post-SAH vasospasm. (A) Axial perfusion CT reveals decreased CBF in the right anterior cerebral artery (ACA) territory (arrows). (B) There is slightly prolonged MTT (arrows). (C) There is a correspondingly decreased CBV (arrows). These findings suggest infarction. (D) Subsequent anterior-posterior view from right internal carotid artery (ICA) angiogram shows severe spasm involving the right ACA (arrows). Axial CT (inset) shows infarction in the right ACA territory (black arrows) and intraparenchymal and subarachnoid hemorrhage (white arrows) from aneurysm rupture.
PWI is usually performed in conjunction with diffusion-weighted MRI (DWI) and assessment of apparent diffusion coefficient (ADC) values. This combination of techniques can differentiate ischemic from infarcted tissue and predict the death of ischemic tissue if reperfusion does not occur (1,20-22). In one report, these techniques were used to guide intra-arterial thrombolytic therapy. Areas of abnormal diffusion are usually assumed to represent irreversible infarction. If the PWI abnormality is larger than the area of restricted diffusion (diffusion/perfusion mismatch), then the region with normal diffusion, but abnormal perfusion, is called “the ischemic penumbra” (Fig. 3). If flow is not restored to the penumbra, the diffusion abnormality will presumably increase in size to include much of the area of perfusion abnormality (1,20-22). More recent studies, however, have shown a more complicated process. The diffusion changes may be partially reversible in patients undergoing successful recanalization with intra-arterial thrombolysis such that the penumbra includes not only the area of diffusion/perfusion mismatch, but also part of the area of restricted diffusion (24-26). There have also been reports of initially normal diffusion in patients presenting within 4 hours of symptom onset who eventually went on to documented infarction. Thus, negative DWI does not exclude impending infarction. However, several of these patients had abnormal perfusion parameters at the time of initial imaging (27,28). Also, there is no consensus as to which perfusion parameter or combination of parameters best defines the penumbra, although a decreased CBV likely indicates tissue that is destined to infarct (1). No studies have been performed to assess whether any perfusion or diffusion parameters indicate risk of hemorrhage with thrombolysis.

PWI has had limited use in other clinical settings. There are some published reports describing its use in assessing patients with chronic cerebrovascular disease, including with acetazolamide challenge to evaluate cerebrovascular reserve (29-32). The use of PWI in evaluating patients with post-SAH vasospasm and during carotid BTO has also been limited (33,34).

DWI and PWI are relatively time-consuming, requiring 15 to 20 minutes of imaging time, even with limited stroke imaging protocols, and they are generally less available and more expensive than CT (1). It is often difficult to adequately screen acutely ill stroke patients for contraindications to MRI and difficult for such patients to cooperate with the relatively protracted examination. Additionally, monitoring patients in the MR scanning environment can be problematic. For most clinical uses, relative, not absolute, quantitative perfusion maps can be obtained with MRI techniques. However, this method permits imaging of the entire brain, gives information not only on perfusion, but also on the status of tissue viability via DWI and can assess vascular patency if MRA is added. No ionizing radiation is used, and there are usually fewer contraindications to gadolinium contrast agents than to iodinated contrast.

**POSITRON EMISSION TOMOGRAPHY**

PET studies using $^{15}$O oxygen tracers have often been considered the gold standard in the assessment of cerebral perfusion (35). Quantitative values can be obtained for CBF, CBV, oxygen extraction fraction (OEF), and cerebral metabolic rate for oxygen consumption (CMRO$_2$), providing an assessment of energy metabolism as well as cerebral perfusion (35). PET studies have defined the penumbra as an area with severely reduced CBF, increased OEF (more than

![FIG. 3. DWI and PWI of a diffusion-perfusion mismatch. (A) Axial DWI shows a small area of restricted diffusion (arrow) in the right periventricular white matter compatible with infarction. (B) Axial MTT map from MR perfusion examination reveals a larger area of prolonged MTT (arrows) encompassing much of the right middle cerebral artery (MCA) territory. These findings are compatible with a large diffusion-perfusion mismatch. (C) There is a correspondingly increased CBV (arrows) on the CBV map indicating that much of this tissue is still potentially viable.](image-url)
0.7; normal, 0.4), and relatively preserved CMRO₂ (more than 1.4 mL·100 g⁻¹·min⁻¹ = 60 μmol·100 g⁻¹·min⁻¹), a pattern called “misery perfusion” (35,36). Although the results vary somewhat among authors, the penumbra likely lies between CBF values of approximately 12 mL·100 g⁻¹·min⁻¹ and 22 mL·100 g⁻¹·min⁻¹. Some studies have indicated that tissue with CBF of as low as 7 mL·100 g⁻¹·min⁻¹ may recover. In PET studies, penumbral tissue has been identified up to 48 hours after symptom onset (35,36). PET studies using tracers other than ¹⁵ oxygen, such as ¹¹C-flumazenil (FMZ) or ¹⁸fluoromisonidazole, may be helpful in distinguishing irreversibly damaged tissue from potentially salvageable tissue (37,38). Although PET studies have shown improved flow in response to thrombolytic therapy, PET has not been used to help select patients for thrombolysis or assess the risk of hemorrhage from such therapy (39).

PET has proven to be more useful in the assessment of patients with known cerebrovascular disease who have not yet had complete infarction, particularly those with carotid occlusion. Up to 60% of patients with carotid occlusion may be asymptomatic because of adequate collateral circulation. PET studies in patients with symptomatic carotid or middle cerebral artery occlusion have shown that an increased OEF is an independent risk factor for stroke (15). It is still unknown whether improving this parameter through revascularization procedures would lead to a decrease in stroke risk (15,40).

PET has also been used in a wide variety of additional clinical settings, including SAH and carotid BTO. It may be helpful in assessing impaired oxygen metabolism in patients with post-SAH vasospasm (41). PET imaging obtained during temporary carotid BTO may be helpful in predicting the adequacy of flow after permanent occlusion (42).

Although PET is the oldest and best validated perfusion imaging technique, its use in routine clinical settings is limited. Many hospitals lack PET imaging facilities. Even if these facilities are available, they are rarely available after hours. PET is a complex imaging technique requiring multi-tracer applications and a cyclotron to produce the radiotracers (35). There is exposure to significant radiation doses (43). Quantitative results require arterial blood gas sampling which is contraindicated in patients receiving thrombolytic therapy (35).

**SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY**

SPECT CBF imaging is obtained using ⁹⁹mTc as the radioisotope attached to hexamethylpropyleneamine (HMPAO) or ethyl cysteinate dimer (ECD) (1). These tracers cross the blood-brain barrier and localize in the brain tissue in proportion to blood flow at the time of injection. Imaging can be performed up to several hours after injection (44). With this semiquantitative technique, activity in an infarcted area is compared with a presumably normal area in the contralateral cerebral hemisphere or to the presumably unaffected cerebellum (1). SPECT is a well-established technique with sensitivity of 61%-74% and a specificity of 88%-98% to abnormal perfusion in acute stroke (45). It is better at detecting cortical infarcts than smaller infarcts involving deep perforating vessels. The threshold of relative CBF between infarcted and viable tissue is between 0.48 and 0.52 in patients not receiving thrombolytic therapy (45,46). SPECT studies evaluating perfusion in patients undergoing thrombolytic therapy indicate that assessing the degree of perfusion of ischemic tissue may be a more useful guide to treatment than the duration of symptoms. Among patients receiving intraarterial thrombolysis, relative CBF thresholds for reversibility of ischemia and for hemorrhage after such therapy were 0.55 and 0.35, respectively, in one study (47).

SPECT has been used in conjunction with an acetazolamide challenge to assess hemodynamic impairment in patients with chronic cerebrovascular disease. This requires performing two examinations separated by one or more days and assumes that CBF does not change significantly between the two tests. Relative (but not absolute) flow values can be obtained. Ratios of CBF that indicate an increased risk of stroke have not been defined (1). Likewise, SPECT has been used during carotid BTO, with the radiotracer being injected while the balloon is inflated. Imaging can be obtained within several hours to document the relative CBF at the time of balloon occlusion. However, no threshold value of lowered CBF indicating inadequate collateral circulation has been determined (1). There have been limited reports of the use of SPECT in patients with possible post-SAH vasospasm (1). SPECT imaging is relatively accessible; most large radiology departments have the appropriate hardware and software (1). But it may be difficult to acquire the kit required to make the injected compound on an emergent basis (1,45). A low resolution technique compared with MRI and CT, SPECT provides little anatomic detail so that it is necessary to correlate the findings with a higher-resolution imaging modality. Because it is only a semiquantitative technique, it requires comparison to the contralateral “normal” hemisphere (1). Relative CBF is the only parameter that can be measured with this technique.

**XENON COMPUTED TOMOGRAPHY**

Xenon (Xe) is an inert gas that is soluble in both water and lipid. X-ray attenuation by Xe is similar to that of iodine, so Xe can be used as a contrast agent in conjunction with CT (XeCT) (1). The gas dissolves rapidly in blood after inhalation and diffuses rapidly into the brain (1,48).
Diffusion into the brain is determined by blood flow and solubility of the Xe within different brain compartments (48). Patients inhale a mixture of 26%-32% Xe mixed with \( \text{O}_2 \) over a period of approximately 4.3 minutes. Processing of the data allows generation of \( \text{CBF} \) maps, from which quantitative data can be extracted (1,48). Multiple studies have validated the accuracy of \( \text{CBF} \) values obtained with XeCT (49,50). In acute ischemia, \( \text{CBF} \) values greater than 20 \( \text{mL} \cdot 100 \text{~g}^{-1} \cdot \text{min}^{-1} \) are associated with sustained viability and reversible neurologic deficit; \( \text{CBF} \) values less than 10 \( \text{mL} \cdot 100 \text{~g}^{-1} \cdot \text{min}^{-1} \) correlate with eventual infarct volume. \( \text{CBF} \) between 10 - 20 \( \text{mL} \cdot 100 \text{~g}^{-1} \cdot \text{min}^{-1} \) has been associated with neurologic deficits that have been reversible with aggressive revascularization procedures or with infarction if no revascularization occurred (51,52). A \( \text{CBF} \) of less than 15 \( \text{mL} \cdot 100 \text{~g}^{-1} \cdot \text{min}^{-1} \) has been associated with an increased risk of edema and brain herniation, as well as hemorrhage after thrombolytic therapy (53,54).

Paired XeCT studies obtained before and after an acetazolamide vasodilatory stimulus have been used to assess hemodynamic impairment in patients with chronic ischemia. Decreased vascular response to the acetazolamide indicates pre-existing vasodilatation and loss of normal autoregulatory vascular reserve (Fig. 4). A decrease in \( \text{CBF} \) values after acetazolamide administration indicates a high risk of subsequent stroke (16,17,55). XeCT has also been used to identify the presence of ischemia (defined as \( \text{CBF} \) less than 20 \( \text{mL} \cdot 100 \text{~g}^{-1} \cdot \text{min}^{-1} \)) in patients with post-SAH vasospasm and has been used to document improved \( \text{CBF} \) after medical or endovascular therapy (56-58). In the setting of carotid BTO, XeCT has been used to help identify patients who clinically pass the BTO but have \( \text{CBF} \) less than 30 \( \text{mL} \cdot 100 \text{~g}^{-1} \cdot \text{min}^{-1} \), placing them at increased risk of stroke (59-62). Adding acetazolamide may help identify patients who exhaust their cerebrovascular reserve during the BTO (62).

XeCT is not only a quantitative method of \( \text{CBF} \) analysis, but this technique is standardized for a given CT system and between different systems (1). Being an inert gas, Xe cannot cause allergic reactions, but at the concentration used for XeCT, it can cause mild sedation, sensory changes, and nausea (63). Despite the widespread availability of standard CT scanners, the relatively low cost of the additional equipment needed to perform XeCT examinations, and the extensive medical literature pertaining to its role in evaluating cerebrovascular diseases, this technique has not had extensive use in the United States (1,45). Patients with neurologic impairment often cooperate poorly for the examination, during which they must inhale the Xe gas through a face mask or mouthpiece. Patient motion can produce artifacts that hamper interpretation (1). \( \text{CBF} \) is the only parameter that can be measured with XeCT (1). Currently there is no commercial supplier of medical grade Xe approved by the Food and Drug Administration; use of the agent is available only under Investigational New Drug authorization (1).

CONCLUSION

Among the many perfusion imaging techniques, PWI and PCT are the two most frequently used in clinical practice. PCT can be performed rapidly and has the potential for wide availability, whereas PWI is a more time-consuming procedure and less readily available, but when used in

FIG. 4. Chronic left MCA ischemia as demonstrated by XeCT. (A) Axial XeCT shows minimally diminished CBF in the left hemisphere (arrows) compared with the right hemisphere. (B) After acetazolamide administration, the axial XeCT CBF map shows a normal increase in CBF in all territories except that of the left MCA, where the CBF decreases, compatible with a steal phenomenon from maximally dilated left MCA vasculature. (C) After a left external carotid to internal carotid artery bypass, the axial XeCT CBF map demonstrates more symmetrical flow between the hemispheres than in (A). (D) After acetazolamide administration, the axial XeCT CBF map now shows a normal increase in CBF in all territories, indicating restoration of vascular reserve in the left MCA territory.
conjunction with DWI, it may provide a relatively simple means of differentiating ischemic penumbra from ischemic core. The use of older and more validated PWI techniques is hampered by their limited availability.

REFERENCES


Some 5,730 abstracts were presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) on May 1–5, 2005 in Ft. Lauderdale, Florida. Available on www.arvo.org, the abstracts are referenced by program number (#). In his keynote address, Elias A. Zerhouni, MD, director of the National Institutes of Health, laid emphasis on eye diseases related to aging and stressed that more research was needed in the field of nanotechnology.

NEUROPROTECTION AND RETINAL GANGLION CELLS

New approaches to neuroprotection that target the optic nerve or the retinal ganglion cells (RGCs) in patients and animal models of optic nerve damage were presented. An experimental optic nerve crush model in rats was shown to produce an early increase in superoxide levels in RGCs, and the authors concluded that scavenging superoxide or inhibiting its intracellular targets may be a useful approach for RGC neuroprotection (#154). Sprague-Dawley rats were exposed to optic nerve crush at different time intervals after traumatic brain injury (TBI) to the contralateral hemisphere to study the effect of TBI on RGC survival. TBI is anticipated to cause immune-mediated neuroprotection and to salvage dying RGCs if performed one to two weeks before optic nerve crush but not concomitantly with the crush. The authors believe that TBI at a distant site may have a neuroprotective effect on the RGCs. This neuroprotective effect is probably immune mediated (secondary to an increased level of brain-derived neurotrophic factor [BDNF]); systemic corticosteroids may aid this neuroprotective effect (#666).

Culture of immuno-purified RGCs was performed to screen for compounds promoting RGC survival. The authors found more than 30 candidate compounds of 1,200 screened and identified a novel pharmacologic compound that promoted RGC survival and neurite outgrowth in a dose-dependent manner (#170).

Neuroprotective agents like LINGO-1 (a new member of the myelin receptor complex), estrogen, copolymer-1, pituitary adenylate cyclase-activating polypeptide, pigment epithelium derived growth factor, inactivation of Rho, and pitavastatin (a statin with high affinity to vascular endothelium) were found to prevent RGC degeneration or promote survival of retinal ganglion and pigment epithelial cells in animal models (#157,158,160,164,167,174,179).

OPTIC NEUROPATHY

The relative risk for obstructive sleep apnea (OSA) was found to be five times higher in patients with non-arteritic anterior ischemic optic neuropathy (NAION) compared to the general population (#644). The rate of OSA was 1.5–2 times more frequent than other risk factors associated with NAION.

The relationship between visual field loss and intraocular pressure (IOP) was studied in patients with optic disc drusen (#658). In 22 patients with intraocular pressure ≥22 mm Hg, 91% had visual field loss. In 81 patients with normal IOP (<22 mm Hg), 66% had visual field loss.

Histopathologic evidence of subclinical involvement of peripheral neurons was found in a patient with Leber hereditary optic neuropathy (LHON) (#661). Neurodegenerative morphological changes affecting most nerve fibers in the brachial plexus were identified.

Optic nerve crush leads to an increase in hydrogen peroxide levels in cultured RGCs with a peak level 3 days after injury (#154).

Antioxidant protein superoxide dismutase gene transfer to mitochondria in an experimental model for optic neuritis transiently protects against oxidative injury to RGC axons (#1197).

The gene defective in dominant optic atrophy (DOA) is OPA1, which encodes a mitochondrial protein implicated in mitochondrial fusion and maintenance of cristae function. OPA1 is a dynamin-related GTPase and may act as a mechano-enzyme or regulatory GTPase. Knockout of OPA1 protein expression in mice triggered a dramatic breakdown in the filamentous interconnected mitochondrial network into multiple isolated organelles (#5188). This was accompanied by partial inhibition of respiration, a decrease in cellular adenosine triphosphate level, and mitochondrial...
ultrastructural abnormalities, which may impair normal neuronal function and lead to degeneration.

**VISUAL CORTEX**

The use of optical coherence tomography to image the retinal nerve fiber layer to identify transsynaptic degeneration in occipital infarcts was explored (#616). Loss of the nerve fiber layer in the nasal hemi-fovea temporally and the horizontal projections nasally was observed in one eye, whereas thinning in the superior and inferior temporal arcades was observed in the other eye in a patient with a homonymous hemianopia.

**BLEPHAROFPASM**

Modulation of photophobia in essential blepharospasm with chromatic lenses was studied (#617). Of seven lenses tested, the FL41 lenses, which block the highest wavelength in the visible spectrum, did not result in the highest intensity of light tolerance compared to other chromatic lenses. However, FL41 lenses were subjectively preferred by most patients with blepharospasm. The authors concluded that photophobia may be related more to wavelength than intensity of light exposure.

**NEUROIMAGING**

Diffusion tensor imaging (DTI) was used to investigate apparent diffusion coefficient (ADC), a measure of diffusion magnitude, and fractional anisotropy (FA), a measure of preferential directionality, as part of MRI scanning of four patients with optic neuritis (#639). Three patients with a good prognosis for visual recovery had high ADC and low FA within one week of visual symptom onset. At three-month follow-up, ADC returned to normal. DTI may provide information useful for predicting the prognosis for visual recovery in optic neuritis. Eyes with high ADC during the acute phase had a good prognosis.

**PSEUDOTUMOR CEREBRI**

The localization of retinoic acid receptors and cellular retinoic acid-binding protein in human arachnoid granulation tissue in vivo and in tissue culture suggests a role for vitamin A in cerebrospinal fluid (CSF) flow regulation (#627). An in vitro model of CSF flow accurately replicated one-way CSF flow and may be used to study idiopathic intracranial hypertension (#629).

**LEBER HEREDITARY OPTIC NEUROPATHY**

A separate session dedicated to LHON detailed the results of a comprehensive 2-year follow-up examination of the 300-member homoplasmic 11778 LHON pedigrees of seven generations described in rural Brazil. Studies of the asymptomatic carriers of the LHON mutation in the Brazilian pedigree reveal that subtle defects, such as nerve fiber layer swelling and telangiectasias, precede the onset of severe vision loss (#1199).

In a rodent model of LHON, an adenovirus was intravitreally injected to deliver a vector containing a mutated form of the ND4 subunit of mitochondrial complex I (#1198). Three months after injection, the rodent had developed optic disc pallor, apoptotic RGC loss, retinal thinning, gliosis, and demyelination. These findings support a role for reactive oxygen species-related injury to mitochondrial proteins in the pathogenesis of LHON.

**ELECTROPHYSIOLOGY**

Near-infrared spectroscopy, which measures changes in hemoglobin concentration evoked by brain activity, showed decreased activation of the visual cortex in patients with unilateral optic neuritis (#640).

Multifocal visual evoked potential testing (MfVEP) was able to demonstrate subclinical episodes of optic neuritis (#641). MfVEP was also used to compare latencies in patients with ischemic optic neuropathy and optic neuritis (#642). Both groups of patients had significantly delayed latencies compared with normal controls. In cluster analysis, the latencies were greater in optic neuritis than in ischemic optic neuropathy.

**PUPIL**

As measured by an automatic pupillometer, pupillary light reflex latencies were greater and amplitudes were lower in the active and recovery phases of patients with retrobulbar neuritis as compared with control subjects (#634).

**PERIMETRY**

In patients with NAION, the number of abnormal points was greater with the frequency doubling than with the Swedish Interactive Thresholding Algorithm technique (#643).

**EYE MUSCLES/MOVEMENTS**

A ring-sling computational model of active rectus muscle pulleys confirmed the active pulley hypothesis and Listing's law of ocular torsion that proposes that the rectus pulleys receive insertions of orbital layers of rectus extraocular muscles (EOMs) to shift pulleys anteroposteriorly during EOM activity so as to maintain a constant distance from pulleys to scleral insertions (#4675). In another paper, this “active pulley hypothesis” was refuted by clinical, imaging,
and physiological evidence (4766). Novel drug delivery techniques, such as single injections of growth factors into rabbit rectus muscles, resulted in an increase in force generation that can potentially be used clinically to increase EOM strength.

It is known that EOMs remain clinically and pathologically spared, even in advanced cases of Duchenne muscular dystrophy (DMD). Quantification of stem cell fractions in mice EOMs and tibialis anterior demonstrated that the proportion of stem cells was increased 5- to 20-fold in EOMs as compared with tibias anterior muscles. This finding supports the hypothesis that EOM stem cells contribute to sparing of EOMs in DMD (5726). In another experimental study in rabbits, the authors found a greater preponderance of stem cells and satellite cells in the EOMs than in limb muscles (4679).

To study the mechanisms of complement-induced neuromuscular junction injury in myasthenia gravis (MG), the authors induced experimental autoimmune MG in mice by injecting rat anti-acetylcholine receptor monoclonal antibodies. They found a significant change in the expression of 204 genes in the experimental mice that encode for immunoglobulin chains, transcription factors, and transport proteins. These pathways may thus be used to study sites for future intervention (5729).

Ultrastructural and immunohistologic studies in experimentally induced hyperthyroid EOMs in mice demonstrated an interstitial protein-like infiltrate, cyclooxygenase-deficient-succinate dehydrogenase-positive muscle cell infiltration, and numerous abnormal mitochondria. These results suggest that mitochondria may play a significant role in the pathogenesis of ophthalmic manifestations in hyperthyroidism (5730).

**ORBIT**

Porous polyethylene implants containing embedded titanium mesh were found to be an excellent alternative to traditional porous polyethylene implants when postoperative imaging of the implant was important (5717).

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There were 1,405 scientific papers and poster presentations at the 57th Annual Meeting of the American Academy of Neurology held in Miami Beach, Florida from April 9 to 16, 2005. Abstracts are published in Neurology 2005;64:Suppl 1. We have summarized the material of most interest to neuro-ophthalmologists.

**OPTIC NEURITIS AND MULTIPLE SCLEROSIS**

Brain MRI is an established biomarker of disease in multiple sclerosis (MS), and data on the impact of MS and acute optic neuritis on retinal nerve fiber layer (RNFL) thickness, as measured by optical coherence tomography (OCT), are beginning to emerge. A recent investigation examined the relation of visual function to RNFL thickness and brain MRI parameters in an MS cohort. Scores for low-contrast letter acuity (Sloan charts) and contrast sensitivity (Pelli-Robson), the leading candidates for visual components for inclusion in the MS functional composite, were significant predictors of average overall RNFL thickness \( (P < 0.001) \) and of lesion burden on T2-weighted MRIs \( (P = 0.001 \) for Sloan charts; \( P = 0.03 \) for Pelli-Robson) accounting for age. The greatest reductions in RNFL thickness were noted among eyes of MS patients with a history of acute optic neuritis. However, MS eyes without an optic neuritis history also demonstrated abnormalities. These results not only confirm a role for axonal loss in the anterior visual pathways of MS patients but demonstrate correlations of low-contrast letter acuity and contrast sensitivity with structural biomarkers, supporting their validity as clinical trial outcome measures (Wu GF, Philadelphia, PA, P01.025).

Visual dysfunction is a common manifestation of MS and may therefore have important effects on health-related quality of life (HRQOL). The 25-Item National Eye Institute Visual Function Questionnaire (VFQ-25) has been used in a variety of ocular conditions and ophthalmic clinical trials. A study was performed to examine whether a 10-Item Neuro-Ophthalmic Supplement could increase the capacity of the VFQ-25 to capture self-reported visual dysfunction in patients with neuro-ophthalmic disorders, particularly those associated with diplopia or optic neuropathy. Patients included those with optic neuritis, MS, idiopathic intracranial hypertension, ischemic optic neuropathy, ocular myasthenia gravis, thyroid eye disease, and ocular motor palsies. Scores for the VFQ-25 + 10-Item Neuro-Ophthalmic Supplement (combined scores) had a greater capacity to distinguish neuro-ophtalmically impaired patients from disease-free controls \( (\text{receiver operating characteristic [ROC] curve area, 0.77}) \) than did the VFQ-25 alone \( (\text{ROC curve area, 0.73; } P = 0.001) \). VFQ-25 + Supplement scores correlated significantly with binocular and with worse eye visual acuities \( (r_s = 0.38 - 0.41; P < 0.0001) \), and Neuro-Ophthalmic Supplement items demonstrated appropriate levels of reliability. The 10-Item Supplement is a valid measure of self-reported visual dysfunction in neuro-ophtalmically impaired patients. This new scale captures symptoms and limitations related to diplopia and will be used to complement the VFQ-25 in clinical trials and other research (Balcer LJ, Philadelphia, PA, P01.031).

Sixty MS patients were studied to establish the relationship of infections to MS exacerbations. MS attacks occurring between two weeks before and five weeks after an infection were considered temporally related to infection. A total of 127 infections were recorded in 53 patients, and 124 exacerbations occurred in 49 of the 53 patients. There was an increased risk of relapses temporally related to infection \( (\text{odds ratio, 3.2; } P < 0.0001) \). Exacerbations that were temporally related to infection were more frequently associated with severe and sustained deficits than those that were not temporally related to infection. The number of Gd-enhancing lesions was higher during exacerbations temporally related to infection than in those that were not temporally related to infection. This study demonstrates a significant association between systemic infection, risk of MS clinical relapse, and degree of MRI activity (Correale JD, Buenos Aires, Argentina, P03117).

**NEUROMYELITIS OPTICA**

Neuromyelitis optica (NMO) is a severe inflammatory central nervous system (CNS) disorder with a predilection for the optic nerves and spinal cord. Because of the potential overlap with MS with regard to clinical and neuroimaging findings, the diagnostic criteria for NMO have been recently re-examined and revised. These new criteria have modified those published in 1999 (Wingerchuk et al., Neurology 1999;53:1107–14) to update MRI findings and to incorporate a novel serum autoantibody marker, NMO-immunoglobulin (Ig)G. Investigations for these
studies calculated sensitivities and specificities for each component of the 1999 NMO diagnostic criteria using a new 118-patient cohort. Combinations of individual criteria, including NMO-IgG, were tested to optimize the potential for correct diagnosis. Among patients with NMO (n = 84) versus MS (n = 34), criteria that had the greatest capacity to distinguish NMO from MS were the presence of NMO-IgG (sensitivity, 75.3%; specificity, 93.3%) and spinal cord T2 lesion length extending beyond three vertebral segments (sensitivity, 97.0%; specificity, 79.0%). Neurological symptoms indicating disease outside the optic nerves and spinal cord were seen in 17 NMO patients (20.2%). Based on these findings, the authors suggested criteria for diagnosis of NMO. Absolute criteria: presence of optic neuritis and acute myelitis (but disease in other areas of CNS allowed); supportive criteria: 1) spinal cord MRI with lesion(s) extending over three or more vertebral segments or 2) NMO-IgG seropositivity (Wingerchuk DM, Scottsdale, AZ, P01.036).

As emphasized by studies refining the diagnostic criteria for NMO (P01.033 above), an NMO diagnosis is no longer precluded by the presence of clinical or imaging abnormalities outside the optic nerves or spinal cord as long as the patient meets the new NMO criteria described the previous paragraph. Importantly, the former (1999) criteria required a normal brain MRI. The brain MRI findings for 60 patients who met revised criteria for NMO (P01.033 above) were described in a recent study. In 26 (43%) of 60 patients, brain MRI was normal at a median of 1.6 years (range, 0–29 years) after the onset of symptoms. Seventeen patients (28%) had non-specific abnormalities that were generally located in the deep white matter and few in number (only four [6.5%] patients had more than four high T2 signal foci). Typical MS-like lesions were found in only six patients (10%), five of whom were seropositive for NMO-IgG. The remaining 11 patients (19%) had MRI findings considered atypical for MS; brainstem lesions were seen mostly among children. Because brain MRI abnormalities were noted among ~50% of patients who otherwise had classic findings for NMO, diagnostic criteria have been revised to allow for brain involvement (Pittock SJ, Scottsdale, AZ, P01.036).

Because brain MRI techniques have continued to evolve, atypical findings have been noted more frequently in the brains of NMO patients. Given the contiguity of the hypothalamic regions to the anterior visual pathways, hypothalamic involvement in patients with NMO is perhaps not unexpected. Two patients with otherwise classic features of NMO were described as having hypopituitarism, hyponatremia, and hypothermia. MRI scans revealed new areas of hyperintense signal in the hypothalamus in the absence of other brain parenchymal lesions. Additional similar cases were identified from the literature, and this series again supports revision of the NMO diagnostic criteria to include involvement beyond the optic nerves and spinal cord (Poppe AY, Montreal, QC, Canada, P01.037).

**GENETIC OPTIC NEUROPATHIES**

Patients with Friedreich ataxia (FA) develop optic neuropathies, most frequently after development of gait and limb dysfunction. Sixteen molecularly defined Italian FA patients with quantified GAA were assessed with visual acuity, fundus photos, 30-degree Humphrey visual field, Ishihara color plates, OCT, visual evoked potentials (VEP), and electroretinography (ERG). All patients showed optic nerve damage as assessed by OCT and visual fields. Fiber loss was typically peripheral; decreased visual acuity was present only when central fibers were lost. VEP was altered in eight (56%) of the patients. In six, they were significantly delayed with reduced amplitudes; in three, the responses were absent. ERGs were normal in all patients. The degree of fiber loss, expressed as thickness of the nerve fiber layer as measured by OCT, was significantly correlated with the GAA expansion in the smaller allele of the frataxin gene (P = 0.002; r = −0.69 for the peripheral sectors). OCT was the most sensitive test in showing optic neuropathy (Fortuna F, Milan, Italy, S01.003).

Investigators designed a battery of clinical measures that may be used for outcomes assessment in FA therapeutic trials. FA candidate performance measures, including the timed 25-foot walk, 9-hole peg test, low-contrast letter acuity, and PATA test (a test of speech) were evaluated in a cohort of 131 FA patients at six academic medical centers. Scores for individual components (including vision) and for the combination of performance measures correlated significantly with neurologic disability, activities of daily living, and disease duration (r = 0.40 – 0.89; P < 0.0001). Visual function scores were also found to be lower in the FA cohort compared with disease-free controls, further supporting the inclusion of low-contrast letter acuity in an FA outcomes assessment battery. Given the high proportion of FA patients who progress to a non-ambulatory status in adulthood, inclusion of measures that capture vision, arm function, and speech will ensure sensitivity and applicability throughout the course of disease (Lynch DR, Philadelphia, PA, P01.104).

To further development of an animal model for Leber Hereditary Optic Neuropathy (LHON), mice received intracocular injections of an adeno-associated virus-ribozyme directed against the murine mitochondrial ND4 subunit of complex I. Their ganglion cells showed hyperchromatic cytoplasm and nuclear condensation suggestive of apoptosis. Optic nerves showed secondary demyelination with axonal loss. Transmission electron microscopy revealed swelling and vacuolization of mitochondria with dissolution of cristae. Allotopic expression of a mutant R340H ND4
results in histopathology similar to that of patients with LHON harboring the G11778A mutation in mitochondrial DNA (mtDNA). This is a step further in development of an animal model of LHON (Qi X, Gainesville, FL, S01.001).

In addition to the three most common mtDNA mutations that occur in patients with LHON, novel pathogenetic mutations continue to be discovered. Overlap with other mitochondrial disease phenotypes, such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), has also been described for mutations involving the ND5 subunit of complex I. An Italian family with a maternally inherited LHON phenotype demonstrated an ND5 mtDNA mutation (G13042A/ND5) that was pathogenetic for LHON yet had been previously described in a case of MELAS. This report underscores the potentially variable clinical expression that may occur in the setting of mtDNA mutations and reinforces the need for consideration of a variety of mutations in patients with optic neuropathies consistent with LHON (Valentino ML, Bologna, Italy, P01.029).

An attempt to use neuroprotection to prevent second eye involvement with LHON was reported. In an open-label prospective pilot study, nine patients with one-eye vision loss for less than six months and normal visual function in the other eye were treated with brimonidine purite 0.15% (Alphagan P) four times daily in the unaffected eye for up to two years. Visual acuity was the primary outcome measure. Secondary measures included changes on automated perimetry and quantification of the relative afferent pupillary defect. There were eight men and one woman enrolled, aged 13–54 years (mean, 32 years); eight had the 11,778 lary defect. There were eight men and one woman enrolled, aged 13–54 years (mean, 32 years); eight had the 11,778 mutations and one the 3,460 mutations. Despite normal visual acuity and visual field mean deviations at baseline, seven patients had minimal changes in the central visual field of the study eye. All patients had deterioration of their second eye vision. Topical brimonidine purite in this dosage was unsuccessful in preventing second-eye involvement (Newman NJ, Atlanta, GA, S01.002).

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare syndrome with congenital absence of conjugate horizontal eye movements from birth and a severe progressive scoliosis. It is caused by mutations in the human axon guidance gene ROBO3 that is important in midline crossing during neurodevelopment. Two genetically defined HGPPS patients were studied. One patient underwent structural MRI, and one underwent Brain Stem Auditory Evoked Responses (BAERs). A T1-weighted three-dimensional volume MRI provided anatomical information and was co-registered to the diffusion tensor imaging (DTI) data. Diffusion tensors were calculated from diffusion-weighted images using standard methods. The structural MRI showed reductions in the size of the pons, medulla, and cerebellar peduncles and flattening of the rostral medulla.

Color-coded DTI showed absence of the decussation of the superior cerebellar peduncles and absence of the major crossing fibers representing the trapezoid body at the pontine level, confirmed by the BAER results in the second patient. Supratentorial crossing fibers appeared normal. Mutations in ROBO3 resulted in DTI-defined abnormal midline crossing of several white matter tracts in the hindbrain. This is the first report of the lack of decussation of both the superior cerebellar peduncles and the auditory/vestibular pathways (Sicotte NL, Los Angeles, CA, S01.005).

Two children with severe microphthalmia and one with anophthalmia developed progressive severe white matter degeneration. The patients were unrelated, but parents originated from the same Pakistani village. Workup for known causes of white matter degeneration was negative. The authors propose that this is a novel example of a leukoencephalopathy in which the abnormal cerebral white matter disappears over time (vanishing white matter) (Kanavin OJ, Amsterdam, Netherlands, S65.001).

**IDIOPATHIC INTRACRANIAL HYPERTENSION**

Obesity and weight gain are known risk factors for idiopathic intracranial hypertension (IIH). However, the profiles of body mass index (BMI; = weight [kg]/height2 [meters]) and weight change that are most associated with IIH have not been defined. A recent case-control study designed to pilot a new risk factor questionnaire and to examine patterns of weight gain and obesity has provided new insight. This study included 34 newly diagnosed IIH patients and 41 age-matched controls. As expected, higher levels of BMI were associated with progressively greater risk of IIH in this cohort (BMI, 25–30; odds ratio in favor of IIH = 6.5; BMI 30–35: odds ratio = 19.5; BMI >35; odds ratio = 26.0; P < 0.01, χ2 for trend). Higher percentages of weight gain during the year before diagnosis (or corresponding reference time for controls) were also associated with IIH (5%–10% weight gain: odds ratio = 3.5; 10%–15%: odds ratio = 10.2; >15%; odds ratio = 15.2; P < 0.01). Most interesting was the finding that among patients with moderate weight gain (5%–15%), those with BMIs <30 (ideal or slightly overweight) were at greatest risk for IIH. Results of this study support clinical observations that associate IIH with increasing degrees of weight gain and indicate that weight gain-associated IIH may develop even among patients of ideal or slightly overweight BMI profile (Daniels AB, Philadelphia, PA, P01.032).

**VESTIBULO-CEREBELLAR PATHWAY DYSFUNCTION**

Whereas skew deviation is typically attributed to brain stem lesions that disrupt otolithic vestibular projections to
the third and fourth nerve nuclei, it may also occur in the setting of isolated focal cerebellar lesions. Focal cerebellar lesions were identified in five patients with vertical ocular misalignment who had no evidence of brainstem involvement (or neuromuscular disease). After detailed testing of the vestibulo-ocular reflex, patterns were found that implicate imbalance of the utriculo-ocular reflex as the mechanism for skew deviation (Wong MF, Toronto, ON, Canada, P01.013).

Benign paroxysmal positional vertigo (BPPV) is a common cause of vertigo encountered by neurologists and neuro-ophthalmologists. The assessment and treatment of BPPV has been systematically investigated by several research groups. BPPV is unique among other causes of vertigo in that it results from misplaced otocoria in the semicircular canals. Treatment, therefore, centers on repositioning of the otocoriaal debris within the canals. Among 524 consecutive patients who presented to an emergency department in Italy with symptoms of dizziness, 243 were found to have BPPV that localized by Dix-Hallpike maneuver to the posterior or anterior canals (n = 202), the horizontal canal (n = 35), or the posterior and horizontal canals combined (n = 6). Canalith repositioning treatment (modified in cases of horizontal canal BPPV) produced resolution of vertigo symptoms in all but six patients (Del Colle R, Legnago, Italy, P01.019).

The efficacy of a new treatment maneuver for posterior canal BPPV was also investigated. This new treatment, the Gans Repositioning Maneuver (GRM), is a hybrid of the Semont Libratory Maneuver (SLM) and the Canalith Repositioning Maneuver (CRM). Although these established maneuvers are well tolerated and easily performed on most patients, those with hip problems that may be aggravated by brisk lateral motion during the SLM, and individuals with a contraindication to neck hyperextension (as required in the CRM), need a modified version of these treatments. The GRM consists of the following: 1) the patient is placed in a side-lying position (used in SLM); 2) the patient rolls onto the shoulder opposite the involved ear (with head turned away from involved ear throughout rotation); and 3) the patient is seated upright. Patients with posterior canal BPPV treated with GRM in a recent series (n = 207) experienced resolution in 80.5% of cases after a single treatment; 95.5% resolved with two treatments. Improvement after treatment was reported among 189 (71%) of the 265 treated patients. The survey

One of the most important challenges facing physicians in an emergency room is differentiating peripheral vestibular dysfunction from more serious brain stem causes (cerebellar or medullary infarction) of sudden-onset vertigo and ataxia. An abnormal head impulse sign (HIS) on vestibular testing is thought to provide clinical evidence in favor of a peripheral vestibular etiology. To perform the HIS, the patient fixates a target while the examiner moves the patient’s head rapidly to each side. The occurrence of a refixation saccade during this maneuver is a sign of decreased neural input from the ear ipsilateral to the head turn. (If there is decreased neural input, the eye travels with the head during the high-velocity movement, and a refixation saccade is required to re-fixate the target.) Among 38 study participants (mean age, 64.3 ± 13.1 years), 5 were diagnosed with peripheral vestibulopathy, and 27 were diagnosed with cerebellar infarcts in various vascular territories (19 posterior inferior cerebellar arteries [PICA], 3 superior cerebellar arteries [SCA], and 5 anterior inferior cerebellar arteries [AICA]). Five patients had a lateral medullary syndrome (LMS), one had a pontomedullary infarct, and ten patients had strokes in multiple vascular territories. The HIS was normal in 18 of 19 PICA infarcts, 3 of 3 SCA infarcts, and in all LMS patients who presented initially with isolated vestibular signs. In the three patients with AICA infarcts and abnormal HIS, the abnormal HIS was attributed to involvement of vestibular nuclei or peripheral vestibular nerve ischemia. The authors concluded that a normal HIS tends to exclude pure brain stem/cerebellar stroke in patients with non-specific acute onset symptoms of vertigo and ataxia (Kattah JC, Peoria, IL, P01.018).

The National Health and Nutrition Examination Survey (NHANES) provides cohort data on a large nationally representative sample of the U.S. population. The prevalence of self-reported dizziness among 3,002 men and women aged 40 years old who participated in NHANES from 1999 to 2000 was reported along with the demographic characteristics, relationship to cardiovascular risk factors, and response to treatment for dizziness in this cross-sectional sample. Dizziness within the past year was reported by 771 (26%) of the 3,002 persons screened. The symptoms lasted less than two weeks in 71%, two weeks to three months in 9%, and more than three months in 20% of the persons with dizziness. The prevalence according to age groups was 20% for age 40–59 years, 27% for age 60–79 years, and 40% for age 80 years and older. Compared with persons who did not report dizziness, persons with dizziness were more likely to be women (61% versus 48%, P < 0.05) and to have a higher mean systolic blood pressure (137/24 versus 133/21 mm Hg; P < 0.05). Treatment was instituted in 265 (35%) of the 771 persons with dizziness. It consisted of medication (n = 149), ear surgery (n = 8), other surgery (n = 9), vestibular exercises (n = 33), or other treatments (n = 66). Improvement after treatment was reported among 189 (71%) of the 265 treated patients. The survey
demonstrates that dizziness is a very common neurological symptom that affects over 20 million adults aged 40 years and older in the United States. Approximately 4 million adults will have symptoms that last over three months. A larger sample is required to appropriately diagnose and treat dizziness among adults (Mohammad YM, Columbus, OH, P03.43).

MYASTHENIA GRAVIS

Patients with ocular myasthenia gravis (OMG) experience diplopia and ptosis that may be disabling. Mycophenolate mofetil (MMF) was administered to 31 consecutive patients with OMG at escalating doses to a target of 1.0 g/d. Patients had been on prednisone and were started on MMF because of adverse effects, objection to corticosteroid treatment, or disease progression. Prednisone (40–60 mg/day) was given during MMF dose escalation, and all were tapered off prednisone after stabilization of symptoms. One patient with thymoma underwent thymectomy. During an average follow-up period of 30 months, 84% of patients remained on MMF therapy. Adverse effects, including nausea, vomiting, and diarrhea were noted, but serious infections and cytopenia were not seen, and therapy was generally well tolerated. None of the patients who continued on MMF (26 of 31) developed bulbar or limb weakness within 2 years of onset. Relapses (ptosis and diplopia) occurred in 12 of 31 patients, and they were treated with pyridostigmine. Larger randomized trials are planned to further examine the potential for MMF to treat OMG and to delay or prevent onset of generalized symptoms (Chan JW, Las Vegas, NV, P01.030).

A case of primary CNS lymphoma was reported after 37 months of treatment with mycophenolate mofetil for myasthenia. This is reported as the first such patient in a non-transplant population (Vernino S, Rochester, MN, P01.070).

Cogan’s lid twitch is often touted as a relatively specific clinical sign of OMG, reflecting fatigability of the levator palpebrae muscle. In a series of 35 patients with symptomatic ptosis, sensitivity of Cogan’s lid twitch sign was found to be 30%, consistent with Cogan’s original findings. However, specificity was 91%, the positive predictive value was 25% (present in one of four patients diagnosed with MG), emphasizing that other etiologies for ptosis may be associated with Cogan’s lid twitch sign (Bhatt A, Detroit, MI, P01.026).

Repetitive nerve stimulation (RNS) was performed on the radial nerve recording from the extensor indicis proprius in ten normal controls and ten patients with MG who had a clinical history and examination consistent with the diagnosis of MG and positive acetylcholine receptor antibodies. A larger decrement was found after radial than ulnar stimulation (17.4 % versus 7.4%). Forty percent of subjects demonstrated >10% decrement on radial RNS without significant decrement on ulnar RNS (Rubin D, Jacksonville, FL P03.044).

VISUAL FIELDS

Homonymous hemianopia (HH) is a disabling visual manifestation of hemispheric infarct, hemorrhage, tumor, or head trauma. Any recovery of HH defects is thought to occur within six months of onset, but the natural course of such recovery has not been examined in detail. A series of 111 cases (complete HH in 38% and incomplete HH in 62%; infarctive in 55%, hemorrhagic in 18%, tumorous in 15%, traumatic in 5%, and neurosurgically-induced in 3%) demonstrated improvement or resolution in 63 (55%) cases. The probability of improvement did not correlate with age, type of lesion, or extent of defect, although resolution was seen more often with incomplete defects. Importantly, improvement of visual field was noted to occur after six months in eight patients, providing evidence for spontaneous recovery that may be useful when evaluating the rational and effectiveness of rehabilitative therapies. Whether such prolonged recovery represents true improvement of visual field function or merely increasing capacity to perform visual field testing remains to be investigated (Zhang X, Atlanta, GA, P01.027).

A study looking at the correlation of neuroimaging with congruity of HH was presented. Among 904 patients, 548 (70%) had incomplete HH. Of these, 373 (68%) were congruous, and 175 (32%) were incongruous. There were no significant differences between the two groups with respect to age, sex, and side of the visual field defect. Fifty-five (84%) of 64 unilateral HH and 318 (66%) of 484 unilateral HH were congruous (P = 0.001). Congruity was more common in macular-sparing HH (88%), paracentral HH (82%), and quadrantanopic HH (69%) than in other incomplete HH (35%) (P = 0.001). HH after stroke was more often congruent (72%) than after trauma (55%), tumors (55%), or demyelination (53%) (P = 0.001). Occipital lobe lesions resulted in the most frequent congruity (84.8%). Isolated occipital lesions produced congruous HH in 83%; however, congruity was also seen in 55% of temporal lobe lesions, 40% of parietal lobe lesions, 62% of basal ganglia lesions, 50% of optic tract lesions, and 57% of lateral geniculate lesions. Of the 118 congruous HH cases with follow-up, 7% resolved, 30% improved, 58% remained stable, and 4% worsened. Of the 52 incongruous HH cases with follow-up, 6% resolved, 33% improved, 42% remained stable, and 20% worsened. Perhaps the most useful information from this study is that at least 55% of incomplete HH secondary to lesions of the optic tract and optic radiations will be congruous (Kedar S, Atlanta, GA, S1.006).
RETINA

Four patients treated with whole-brain irradiation for primary CNS lymphoma developed retinopathy. The clinical presentation of retinopathy included blurred vision (2 cases), visual loss (3 cases), and floaters (1 case). One patient was clinically asymptomatic at diagnosis of retinopathy. The median latency from completion of radiation therapy to diagnosis of retinopathy was 25 months. Ophthalmic signs in these patients included retinal hemorrhages (2 cases) and vasculopathy (3 cases). No patient had previous diabetes or other vascular disease (Grimm SA, New York, NY, P01.071).

VISUAL PROCESSING

Change blindness (CB) refers to an inability to detect changes in visual scenes because of a failure to encode information into visual short-term memory (VSTM). A study of CB in a traffic scene in 12 early Alzheimer disease (AD) patients, 13 older control subjects, and 25 younger control subjects was performed. Half of the trials contained a discrete object that gradually faded in and out of the scene and half contained no change. Participants had to determine whether a change occurred. Advanced age and AD reduced the ability to detect and respond to changes in traffic-related scenes, indicative of increased CB. The authors attributed the increased CB in advanced age and AD to declining control over the focus of attention upon items entering VSTM or decreased VSTM capacity. The AD participants in this study were also more likely than control subjects to report a change when none had occurred, compatible with impaired perceptual decision-making. Cognitive decline caused by aging and AD produces increases in CB, which may have consequences for processing key information in a variety of real-world tasks, including automobile driving (McEvoy S, Iowa City, IA, S61.003).

To test the hypothesis that visual and cognitive functions deteriorate along with motor function in Parkinson disease (PD), 61 PD patients were tested on many cognitive, basic, and higher order visual functions. PD patients with mild-moderate disease severity were impaired in basic and higher visual abilities, as well as cognitive functions including attention, memory, and executive functions compared with elderly controls. The higher order visual and cognitive dysfunction correlated with motor severity, in particular with axial/gait impairment, and may contribute to some of the dysfunction in PD patients (Ergun Y, Iowa City, IA, P03.155).

A study compared visual hallucinations in patients clinically diagnosed with AD and patients with Dementia with Lewy bodies (DLB). Hallucinations occurred in 63% of DLB patients and in 8% of AD patients. They occurred earlier in the course of DLB (1.7 years) than in AD (6 years) (Ferman T, Jacksonville, FL, S25.001).

HEADACHE

A case report of episodic posterior hemispheric dysfunction with severe headache beginning 17 years after resection and radiation for a cerebellar astrocytoma was reported. Episodes lasted days to weeks. As part of the syndrome, homonymous hemianopia developed on one side or the other. Electroencephalogram (EEG) showed unilateral occipitoparietal slowing, and MRI revealed unilateral diffuse cortical enhancement on the side corresponding to the homianopia. With resolution of clinical deficits, the EEG and MRI changes resolved. This is the third such reported case after radiation. The authors suggest the acronym SMART for Stroke-like Migraine Attacks after Radiation Therapy (Lachance D, Rochester, MN, P04.048).

STROKE

Patent foramen ovale (PFO) has been implicated as a cause of stroke. Therapeutic options include antiplatelet medications, warfarin, and surgical or percutaneous closure, but there is little rigorously acquired information to support any particular therapy. A survey of cardiologists and neurologists who were about to participate in a clinical trial on PFO treatment showed the following results:

Neurologists recommended antiplatelet medications for 49% (±SD, 33%) of patients, whereas cardiologists recommended them in 26% (±SD, 26%; P = 0.0003). Neurologists prescribed warfarin for 28% (±26%), whereas cardiologists prescribed it in 17% (±22%; P = 0.04). Neurologists chose surgical closure for 23% (±9%), whereas cardiologists only chose it for 0.2% (±0.8%; P = 0.05). Neurologists recommended percutaneous closure for 20% (±21%) of patients, whereas cardiologists recommended it for 54.5% (±33.5%, p < 0.0001). Further, 2% of neurologists and 9% of cardiologists recommended closing asymptomatic PFOs (P = 0.2); 6% of neurologists and 24% of cardiologists recommended closure of PFO for SCUBA diving (P = 0.02). Finally, no neurologists and 14% of cardiologists recommended PFO closure for migraine treatment (P = 0.01). Clearly, there are differences in the practice patterns of neurologists and cardiologists, with the latter more likely to recommend percutaneous closure (Messe SR, Philadelphia, PA, P03.065).

A study of the sensitivity of magnetic resonance angiography (MRA) for posterior communicating artery (PCA) aneurysm was presented. A neuroradiologist masked to the side of the third cranial nerve palsy or suspected aneurysm examined the maximum intensity projection (MIP) images and source images to determine if the PCA vessel itself or a PCA aneurysm was present. Of 201 PCAs, MIP
images showed 106. Source images ($P = 0.0001$) showed 182 PCAs. Source images revealed 42 of 43 aneurysms (missed aneurysm diameter: 2 mm), and MIPs showed 39 (missed aneurysm diameters: 2–6 mm). MRA and catheter angiography aneurysm size measurements were closely correlated ($r = 0.97$). When source image analysis of MRA is used, PCA aneurysms with a diameter of $>2$ mm should not be missed, and the authors suggest that catheter angiography may not be required. Although this may be true, the reliability of the readings clearly relies on the expertise of the person reading the films (Kupersmith MJ, New York, NY, S01.004).

Sleep apnea syndrome (SAS) has been associated with stroke. Recent reports anecdotally link SAS with nonarteritic anterior ischemic optic neuropathy (NAION). One possible explanation is a decrease in blood flow. In a study of 76 consecutive awake SAS patients and 70 control subjects, mean blood flow velocity (MV) and pulsatility index (PI) in the middle cerebral artery (MCA) and basilar artery (BA) were measured by cervical and transcranial Doppler (TCD) ultrasonography. Patients with cervical or intracranial arterial stenosis were excluded. Values of MV in MCA and BA were significantly lower, and PI values were significantly higher in the MCA in SAS patients. This study demonstrates differences in cerebral hemodynamics between SAS patients and healthy subjects, a finding that may explain the relatively higher stroke risk in SAS patients (Segura T, Albacete, Spain, S04.006).

**OCULAR MOTILITY**

Patients with Fisher syndrome have often had neurologic deficits attributable to brain stem damage, leading to confusion with the diagnosis of brainstem encephalitis. A 62-year-old man with ophthalmoplegia and dilated unreactive pupils after pharyngitis demonstrated increased jitter and blocking on single-fiber electromyography (EMG), implying that there is a neuromuscular junction disturbance in Fisher syndrome. Muscle strength was normal. Deep tendon reflexes were reduced. Gait was tentative but normal; tandem walking was difficult. Brain MRI was normal. Spinal fluid protein was normal, and GQ1b antibodies in low titer developed later. Standard EMG and nerve conduction studies were normal (Lange DJ, New York, NY, P03.048).

Oculopharyngeal muscular dystrophy (OPMD) is an inherited myopathy clinically characterized by onset in adulthood of ptosis and dysphagia, often accompanied by extraocular and limb muscle weakness. In nine patients with OPMD, the EMG findings were reviewed to determine whether neuropathy may be part of this disorder. The average age at the onset of symptoms was 51 years, and average age at the time of the EMG was 62 years. Clinical findings included ptosis in nine (100%), dysphagia in nine (100%), limb weakness in nine (100%), ophthalmoplegia in six (66.7%), and distal paresthesias in one (11.1%). All patients had characteristic findings of myopathy; none had findings of neuropathy or neuromuscular junction abnormalities. These findings should be helpful in differential diagnosis because other diseases, including myasthenia gravis, may present with similar symptoms (Jones LK, Rochester, MN, P03.056).

The distinction between epileptic and non-epileptic seizures (NES) can be difficult and may occur in a same patient. The incidence of NES is 5%–20% in an outpatient epilepsy population and up to 40% for inpatients studied at epilepsy centers. Previous studies found that there are some stereotypical movements associated with NES, such as pelvic thrusting and back arching. A study examined eye closure in relation to NES. Among 52 patients with NES, 50 (96%) had their eyes closed during seizures. In contrast, only 4 (3%) of 156 patients with epileptic seizures had their eyes closed during a seizure. Interestingly, many patients with epileptic seizures would have their eyes open even when their seizures occurred during sleep. The authors conclude that ictal eye closure is a highly reliable indicator for NES (sensitivity, 96.15%; specificity, 97.44%). Because it is a simple observation that can be easily reported, ictal eye closure could be a very useful screening question in an outpatient setting (Chung SS, Phoenix, AZ, S30.004).

The eye movement abnormalities in 17 patients believed to have a purely psychogenic disturbance were reported. In this group, 15 had convergence spasm, 1 had opsinclonus, and 1 had blepharospasm. Interestingly, only 7 (41%) of these 17 patients had visual symptoms (diplopia or blindness) as their chief complaint. Non-ocular psychogenic movement disorders were present in 15 (88%). The co-existence of multiple psychogenic signs may be helpful in separating psychogenic from organic eye-movement disorders (Mejia NI, Houston, TX, P01.168).

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The seventh biennial meeting of the European Neuro-Ophthalmology Society (EUNOS) met in Moscow, Russia, on June 26–29, 2005. Hosted by Professor Natalia Eliseeva and Dr. Natalia Serova, with the able assistance of Dr. Natalia Pestovskaya (“The Three Natashas,” as they came to be known) of the famed Burdenko Neurosurgical Institute, the meeting was a wonderful amalgam of keynote lectures, free papers, posters, and exciting discussions. There were 250 attendees, about half from Russia and former Soviet Union countries, the remainder from Europe and the United States. The proceedings were beamed by satellite throughout the former Soviet Union so that physicians who could not be present were able to enjoy the meeting.

There were 11 separate sessions, including neuro­physiology, optic pathway lesions, the optic nerve, eye movements, the pupil, intracranial pressure, imaging (ultrasound, Heidelberg Retinal Tomography, and Optical Coherence Tomography [OCT]), cranio-orbital trauma and tumors, and vascular lesions. Although English was the official language of the meeting, there was simultaneous translation for Russian-speaking attendees. Keynote lectures were delivered by Mikhail Ostrovsky (Moscow, Russia), (the effects of light on retinal degeneration), Angelica Shamshinova (Moscow, Russia) (electrophysiology of the visual system), Christopher Kennard (London, United Kingdom) (saccade generation), Helmut Wilhelm (Tuebingen, Germany) (the pupil and vision), Emmanuel Cabanis (Paris, France) (new neuro-imaging techniques with special reference to diffusion tensor and functional MR imaging), Sergey Eoltchiyan (Moscow, Russia).
Russia) (diagnosis and treatment of cranio-orbital injuries), and Vasily Cherekaev (Moscow, Russia) (skull base tumors involving the orbit and paranasal sinuses), as well as Kathleen B. Digre, MD (Salt Lake City, UT) (idiopathic intracranial hypertension), Mark J. Kupersmith, MD (arteriovenous shunts of the cavernous sinus), Andrew Lee, MD (Iowa City, IA) (lesions affecting the optic tract), and Neil R. Miller, MD (Baltimore, MD) (optic nerve sheath meningiomas).

Free paper highlights included an update on the efficacy of ventriculoperitoneal shunting by Gunnel Bynke (Goteborg, Sweden), a treatise on the anatomy of the subarachnoid space and its influence on papilledema by Hans-Peter Killer (Aarau, Switzerland), an update from Susanne Trauzettel-Klosinski (Tuebingen, Germany) on visual restoration therapy, a presentation by Gordon Plant (London, United Kingdom) on the OCT findings in patients with recovered optic neuritis, and a review of the results of the extremely controversial electrical stimulation therapy for traumatic optic neuropathy by L. Linnik (Moscow, Russia). Other excellent papers included one on the pathology and appropriate classification of the Sturge-Weber syndrome by Cameron F. Parsa, MD (Baltimore, MD), a discussion of the
visual field blocking phenomenon in patients with chiasmal syndromes by Hans Fledelius (Copenhagen, Denmark), and a review of the findings in patients with NF-2 and optic nerve sheath meningiomas by Klara Landau (Zurich, Switzerland).

There was also an excellent social program, beginning with a bus tour of Moscow to open the meeting on Sunday, June 26. The tour included stops at the Kremlin, Red Square, and various historical monuments. A lovely welcome reception at the Burdenko Institute that evening afforded the attendees the opportunity to get to know one another over wine, cheese, and canapés. On Tuesday, June 28, many attendees took in a performance of Don Quixote at the world-renowned Bolshoi theater, which is about to close for several years of renovation. A wonderful farewell party was held at the State Museum of A.S. Pushkin, Russia’s renowned writer, on Wednesday, June 29. The evening featured beautiful music, superb food, and a chance to discuss the week’s activities with colleagues from around the world.

The meeting was one of the most successful and entertaining in the history of EUNOS. Kudos to The Three Natashas for a tremendous experience, Professor Alexander Konovalov and the staff of the Burdenko Neurosurgical Institute for providing the perfect venue, and a special thanks to William F. Hoyt, MD (San Francisco, CA) for opening up this area of the world much as he has other areas throughout his illustrious career! The next EUNOS meeting will be held on May 26–29, 2007 in Istanbul, Turkey and will be hosted by Pinar Aydin (Ankara, Turkey).

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Youmans Neurological Surgery, 5th Edition


Scope: This is the fifth edition of the venerable reference text in neurosurgery.

Since the first edition appeared in 1973 as a single volume, it has grown to four titanic volumes containing more than 5,000 pages, 335 chapters, and 300 authors. The authors, whose photographs and credentials occupy the first 40 pages of Volume One, make up a roster of the “big names” in neurosurgery, related clinical disciplines, and basic neuroscience. It is, therefore, the “official record.” As compared with the fourth edition, which appeared in 1996, this edition is more comprehensive and includes more emphasis on neurophysiology, ancillary diagnostic techniques, and historical development. If something has been left out, I have yet to discover it.

Strengths: Nowhere will you find so much material under one cover (well, four covers) written by so many authorities in the field. Style has been kept quite uniform—a sign of tight editing. Illustrations are generally good, legends are clear, layout is attractive, and references seem to be ample and accurate. Although surgical technique is covered, there is much to read about the preamble to surgery and its complications.

Weaknesses: Given the vast number of authors, many from outside North America, you expect and find considerable variation in writing quality. Readers may find that some neurologic conditions have been oversimplified. Acknowledging how long it takes to bring a work of this size to market, you will not find fast-breaking news.

Recommended Audience: Neuro-ophthalmologists, neurologists, otolaryngologists, maxillofacial surgeons, and others who interact with neurosurgeons will find this the go-to source for compact overviews of topics related to neurosurgery.

Critical Appraisal: Although there are other huge textbooks of neurosurgery, none matches this one for gravitas. In its category, it remains the first choice of neurosurgeons. The editor, H. Richard Winn, MD, former chair of neurosurgery at the University of Washington, is a respected clinician and scientist. He has done an incredible job of recruiting and overseeing the heavyweights in the field. If you do not find something in this encyclopedia, it doesn’t exist.

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Textbook of Clinical Neurology, 2nd Edition


Scope: This multi-authored text is divided into three sections based on the three-step process used by most clinical neurologists in evaluating patients in everyday practice: neuroanatomical localization and syndromes, neurodiagnostic tools, and etiological categories of neurologic diseases. As such, it provides a unique and efficient reference tool that can be used frequently and efficiently. Also included is a CD-ROM containing the full text and still images as well as a number of digital video images illustrating various conditions, including ocular motility abnormalities and movement disorders.

Strengths: The text is organized in exactly the same way clinicians think when encountering patients in the clinic: 1) Where do the symptoms come from? 2) What tests do I need to order? 3) What can cause this, and how can I treat it? Despite the multi-authored approach, the individual chapters are consistently written and organized. With few exceptions, each chapter begins with a historical overview and clarifications of semantics for the topics discussed, followed by techniques for obtaining appropriate clinical history and examination data, anatomic localization strategies, review of clinical syndromes, and concepts of management goals. The text is easy to read and is logically organized.

Weaknesses: As with any broad text, space limitations are inherent. Giant cell arteritis and idiopathic intracranial hypertension receive only two pages each, and skew deviation warrants only a paragraph. Information on neurologic diseases in children is sparse. Neuro-ophthalmologists will likely find the neuro-ophthalmology sections rather basic. For the comprehensive neurologist or ophthalmologist, these areas are a useful summary. There are some obvious errors (incorrect statements about the primary action of the oblique muscles and the applications of pattern visual evoked potentials in children), but they are few. The CD-ROM digital video images are inconsistent in quality; some are almost impossible to interpret on a standard monitor.

Recommended Audience: All neurologists, ophthalmologists, and neuro-ophthalmologists will find large portions of this text quite useful. It may be the best neurology text for internists and primary care physicians.
Critical Appraisal: This is a consistently written, well-organized, clinically useful neurology text that is likely to be frequently used by a variety of practitioners.

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The Central Nervous System: Structure and Function, 3rd Edition

Scope: This is a single-authored textbook on the anatomy and function of the nervous system with an emphasis on clinically relevant anatomy, development, neurophysiology, and neurochemistry. It is replete with black-and-white photographs and red, pink, black, and gray diagrams that beautifully illustrate anatomic points and relationships. The first part of the book is organized in terms of cellular elements, functional properties of neurons, parts of the nervous system, development, aging, and plasticity. The second part is organized by system (sensory, motor, brain stem, auditory, limbic, and cortical). In addition to the basic text, there are shaded boxes with more in-depth commentary. The reader can use the text as a basic clinical textbook, as a topic review, or as a reference book.

Strengths: The book is cohesive and emphasizes clinically relevant points of anatomy and physiology. It is written in a wonderfully accessible style, which makes it an attractive book to read in its entirety. Other basic neuroanatomy textbooks do not really come close to it in terms of its discussion of clinical correlations and functionality in the nervous system.

Weaknesses: There is very little discussion of glial elements and their role in the functioning of the nervous system. In comparison to the three editions of this book authored by the author’s father, there is less emphasis on comparative anatomy and historical descriptions and fine detailed cellular anatomy so prominent in the last century.

Recommended Audience: The book is appropriate for medical students, neurology residents, and psychologists and physical therapists studying the anatomy and organization of the nervous system. It would also be useful for teachers of neuroanatomy as a reference text and for the quality of its plentiful diagrams and charts.

Critical Appraisal: All of the good features of Brodal senior’s editions have been carried on in this edition authored by his son. Moreover, the book is brought into a more modern era with a very strong overview and organization.

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MRI and CT of the Brain

Scope: Edited by two neuroradiologists from The University of Manchester, this multi-authored text covers the normal radiographic anatomy of the intracranial contents, as well as the magnetic resonance (MR) and computed tomography (CT) features of the most common disorders encountered in general neurologic practice. Orbital and spinal cord manifestations of neurologic and neuro-ophthalmologic diseases are not covered.

The book consists of three sections. Part 1, “Atlas of Normal Brain Anatomy,” contains axial CT sections through a normal human brain and multiplanar normal MR images. There are labeled drawings of several anatomic areas of interest and diagrams of the distribution of the major arterial territories. Part 2, “Atlas of Brain Pathology,” outlines the characteristics of major categories of pathology. Part 3, the largest portion of the book, contains ten chapters covering the CT and MR features of the major categories of brain pathology in adults and children.

Strengths: The images are nicely reproduced. They illustrate most of the important CT and MR features of the important diseases. In most cases, advanced rather than early pathology is illustrated. Most of the radiographs are accompanied by a clinical history that adds to the readability of the volume. The discussion of diffusion-weighted imaging and apparent diffusion coefficient mapping is very good, but the illustrations are too few to demonstrate the range of uses of this imaging sequence.

Weaknesses: The section on normal CT and MR anatomy lacks sufficient detail. The labeling is not complete, and the number of images is too few to permit the meticulous localization often required in neuro-ophthalmic practice. Normal coronal MR images are shown without a brain section for comparison. Instead, a midline sagittal MRI is shown with a vertical line indicating the plane of the coronal section. Labeling is sparse, and the sections are widely separated. Normal images are inadequately illustrated. The diagrams show only minimal detail. In addition, the book does not systematically outline the normal signal characteristics of various tissues, such as fat, flowing blood, and
white and gray matter. Coverage is sketchy in many areas of interest to neuro-ophthalmologists. For example, the radiologic characteristics of optic pathway gliomas are not fully described or illustrated. The book does not discuss the imaging characteristics of optic neuritis or optic nerve sheath meningioma or the radiologic evaluation and differential diagnosis of optic nerve enlargement. The clinical utility of the book is also limited by absence of images showing early-stage pathology. Differential diagnosis is rarely offered for any of the images. Finally, CT angiography is not covered, and the book includes very little material on MR angiography.

**Recommended Audience:** The text is designed for trainees and practitioners in any of the neurologic disciplines. It lacks the detail to be of use to trainees or practitioners in neuro-ophthalmology.

**Critical Appraisal:** This book will be of limited value for neuro-ophthalmologists because of the paucity of detail and lack of early-stage pathology.

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**Color Atlas of Neurology**


**Scope:** This is a pocket-sized paperback atlas that is meant to clarify and dramatize neurologic conditions. As such, it borrows heavily on the work of the late Frank H. Netter, the noted medical illustrator. This little volume is packed with information—text, schematics of neural pathways, tables of differential diagnosis, and paintings of patients in various sickly states. Everything seems to be in vivid color, including the margins of the pages, which are color coded to correspond to different sections.

**Strengths:** The artists have used a lot of imagination in depicting disease—in drawing the pathways, the appearance of sick patients, diagnostic tools, wave forms of electroencephalograms, and anatomic and histologic disorders. Inasmuch as pictures are more fun to look at than paragraphs of text, this is an entertaining way to learn.

**Weaknesses:** Some things simply cannot be illustrated in still pictures; for example, consider incontinence, spinal claudication, vertigo, or nystagmus. Some of the art work showing ill patients is downright grotesque. The material is too densely packed; many pages have a dizzying number of illustrations.

**Recommended Audience:** I am not sure who will find this book useful. It is a bit too advanced for non-physicians. Medical students may find some parts a good way to approach or even review some topics. It is likely to be too hokey for house officers or practitioners.

**Critical Appraisal:** This is essentially an introductory textbook of neurology, but the text is secondary to the vast number of Netter-like paintings used as illustrations. The art work is uneven, and most of it is not up to the quality of Netter's work. Many readers will be attracted by the fact that there are more pictures than words but may soon find that most of this material does not easily lend itself to this type of illustration.

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**Form and Function in the Brain and Spinal Cord: Perspectives of a Neurologist**


**Scope:** This book is a reflection of one man's career in neurology and neuroscience. It is an annotated compendium of 34 previously published papers and chapters, each illustrating an aspect of neuroscience or neurology or of the process of being a neurologist or neuroscientist.

The papers are published in the order in which the author became interested in the topics. They reflect a very personal evolution and exploration of the broad field of neuroscience and the inter-relatedness of form and function in the nervous system. The annotations are a commentary on how and why the author became interested in the topic, the goal of the paper or chapter, and its significance in the context of the field of neuroscience.

The papers range from clinical discussions of aspects of higher function to work with the Sternarchus, a fish which generates a reversing electrical field around itself to navigate its environment, to papers concerning the axon in both the central and peripheral nervous system. The large number of papers in this area reflects the author's primary interest in the axon.

The annotations convey the author's delight and fascination with neuroscience. He also analyzes the place of his work in the context of neuroscience and makes broad comments that help the reader understand the importance and place of the paper. For example, he discusses how cells tune their conduction velocity to meet functional needs, how...
sodium channels are deployed in demyelinating segments, how different types of sodium channels have roles in myelinated versus unmyelinated fibers, how channels can interact or act in concert to provide the required signals and responses, the potential use of olfactory and sheathing cells to repair myelin deficits, and how the author found himself interested in pain research through his interest in axonal function.

**Strengths:** As a chronology of a career, this book is a pleasure to read. Many of the articles are highly technical, but the annotations are certainly accessible to those with little training in basic science or neurology. The wide variety makes the book interesting.

**Weaknesses:** Many articles are out of date, and some of them reflect very limited aspects of the total amount of information available about a topic. Even so, many of the older articles are still relevant because they describe valid clinical observations or because they are of historical importance.

**Recommended Audience:** This would be an engaging book for someone considering a career in neuroscience or in scientific research in general. It shows how alive and changing such a career can be; it shows the many roads one may go down as one pursues an area of interest. The annotations would be interesting to a wide audience. The papers themselves are more specialized.

**Critical Appraisal:** This is an interesting book about a fascinating career. The annotations make for enjoyable reading. The papers themselves are elegant and interesting.

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**The Visual Neurosciences**


**Scope:** This is an extraordinary two-volume, 1,700-page compendium of the state of our knowledge of the visual neurosciences written by more than 100 expert researchers in the field. Each chapter was additionally reviewed by other experts before the final version. The goal was for the expert researchers to summarize their area of specialization in a manner understandable to the nonspecialist. The result is a comprehensive and authoritative account of the visual neurosciences that is truly unique in its scope and presentation.

The text begins with two historical chapters, followed by sections on developmental processes, retinal mechanisms and processes, organization of the visual pathways, and projections for subcortical and primary visual cortex processing. Using a molecules-to-pathways-to-systems approach, these first sections provide the anatomic and physiological context for understanding the psychophysical, perceptual, and neurophysiological concepts in the sections that follow, including visual detection and sampling, and the higher-level processing of brightness and color, form, shape, and object recognition, motion, depth, and spatial relations. The contribution of non-sensory variables in visual perception is then considered in the sections on eye movements, attention, and cognition. A final section on theoretical and computational perspectives offers several approaches to the integration of ideas within neuroscience, psychology, and computer science.

There are thousands of black and white figures, most of them original drawings, and many of them superb and easily understood diagrams of pathways and systems. Additionally, there are 85 color plates, half inserted into the center of each volume, of magnificent quality and clarity.

**Strengths:** The contributors to these two volumes are the experts in their fields, reviewed by fellow experts. Yet the language is clear and highly readable. Indeed, this text is an excellent example of the premise that the most complicated subjects can be made simple by those who truly know the material.

**Weaknesses:** There is some overlap across chapters and even dissimilar viewpoints among the experts, but this overlap serves only to highlight those areas requiring further scientific investigation. The prose of some of the authors approaches “folksy” at times, but this too adds to the genuineness of the contributions.

**Recommended Audience:** This is a text not easily read cover to cover, but rather a scientific reference for researchers, students, and the clinical practitioner. It is a must read for all those involved with the visual system.

**Critical Appraisal:** This text is a unique resource. Although there are many journals dedicated to vision research and several texts that summarize specific aspects of the neural bases of vision, no single source provides this degree of comprehensiveness and depth in the visual neurosciences.

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**Sensory Transduction**


**Scope:** This is a single-authored book that reviews the basic anatomy, physiology, and molecular biology of the sensory
systems and cellular signal transduction in primates and humans.

The book is divided into ten chapters. In the first chapter, the author provides a historical review of the contributions of ancient philosophers and poets, nineteenth and twentieth century anatomists and physiologists, and modern molecular biologists. Three chapters are devoted to a review of the different mechanisms of sensation and receptors, channels, electrical signaling, and intra-cellular signal transduction. In the next five chapters, the author reviews each sensory system separately, including mechanoreceptors and touch, hairy cells and detection of movement (the vestibular system), sound, chemoreception and the sense of smell, taste, and photoreception. The last chapter of the book is devoted to the biology of the extrasensory receptors, including thermoreceptors.

Strengths: The striking feature of this book is its simplicity. The writing is clear, and chapters are organized with abundant illustrations. Readers will not be confused or overwhelmed by details of molecular biology and physiology. The author cleverly uses simple pictures and illustrations to explain cellular signaling.

Weaknesses: Some of the information included is too “scientific” for clinicians. Much of the book seems more directed at basic science researchers.

Recommended Audience: This book is extremely valuable for students, residents, basic scientists, researchers, and clinicians to learn complex mechanisms of sensory system and cellular signal transduction. Neurologists, ophthalmologists, and otolaryngologists should at least read the chapter devoted to their sensory systems.

Critical Appraisal: This is a well-written book that will improve our understanding of the sensory organs and their precise functions.

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Handbook of Stroke Prevention in Clinical Practice


Scope: This handbook, another addition to the classic series Current Clinical Neurology, is a multi-authored textbook providing a useful update on stroke risk factors. There are numerous useful tables and definitive summary statements regarding vascular risk factors and available interventions. An accompanying CD-ROM can be downloaded into a computer or PDA. The book is divided into 17 chapters. The first two present epidemiology and classification of stroke. The next 15 chapters focus on risk factors for stroke.

Strengths: This is a comprehensive review of risk factors for stroke. Recommendations for screening and treatment are provided, and multiple tables help the reader. Summaries are provided at the end of each chapter, often with a table.

Weaknesses: This is all text; there are no illustrations. One’s first impression is that this will make it difficult to read. Actually, it reads easily!

Recommended Audience: Anybody interested in stroke and in vascular disease should read this book. It is accessible to medical students as well as to stroke neurologists or cardiologists.

Critical Appraisal: The authors have been able to present difficult information in a clear, concise, yet comprehensive fashion, making this small book precious to the practicing physician.
Brown Syndrome Associated with Morning Glory Syndrome

A 4-year-old girl presented with a left esotropia that had been noted by her parents since birth. There was no family history of ocular disease or of maternal drug use during pregnancy. Visual acuity was 20/20 OD and hand movements OS. She had a left esotropia of 16 prism dipters, a deficiency of elevation-in-adduction, and an ocular down shoot in adduction bilaterally, findings considered classic for Brown syndrome. She also had bilateral superior oblique overaction (Fig. 1). Ophthalmoscopy was normal OD and showed an enlarged and excavated papilla with an elevated peripheral pigmented choroid and a spoke-like arrangement of retinal vessels emerging at the disc margin OS, the classic findings of morning glory syndrome (Fig. 2).

Brown syndrome is caused by an abnormality in the superior oblique tendon-trochlea complex. Forced duction testing is required to confirm the diagnosis, but lack of cooperation makes it difficult to perform this test in very young patients. In these patients, it can be diagnosed based on the typical poor elevation-in-adduction with the frequently associated down shoot of the affected eye in adduction. An overacting superior oblique has been noted in some cases (1). The syndrome is usually unilateral and congenital but may be acquired. In congenital form, the etiology is unclear. Familial occurrence has been noted, but most cases are sporadic. Although Brown syndrome is usually an isolated finding, co-existence with crocodile tears, congenital ptosis, Marcus Gunn syndrome, and coloboma of the choroid has been reported (2). In a study of the trochlear region in the fetus and embryo, Sevel (3) proposed that persistence of thickened embryological trabeculae might result in Brown syndrome.

Morning glory syndrome is a rare congenital anomaly of the optic disc, including an enlarged and excavated papilla with an elevated peripheral pigmented choroid and a spoke-like arrangement of retinal vessels emerging at the disc margin. Most cases are unilateral, and visual acuity is usually poor in the affected eye. The etiology of the anomaly is unknown, and no hereditary tendency is evident. Usually an isolated anomaly, some cases have also had persistent hyperplastic vitreous, ciliary body cyst, congenital cataract, and midline craniofacial defects such as basal encephalocele, hypertelorism, cleft lip and palate, or agenesis of the corpus callosum. The association with midline craniofacial anomalies has been attributed to a developmental defect in embryogenesis during the second gestational month (4).

In a report of Duane retraction syndrome, another largely sporadic ocular motility disorder, which was associated with morning glory syndrome (5), the authors speculated that a disturbance in embryogenesis at about two months of gestation was responsible for that rare association.

This case appears to be the first report of the association of Brown syndrome and morning glory syndrome.

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FIG. 1. Brown syndrome. The patient displays left esotropia, bilaterally reduced supraduction-in-adduction, down shoot in adduction, and overaction of the superior oblique muscles.
Further studies are required to determine whether the association is merely coincidental.

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REFERENCES

Erratum
For the article “Reversible Carotid Artery Narrowing in Morning Glory Disc Anomaly” in the September 2005 issue of this journal, an author’s name was incorrectly printed as Donald J. Easton. The correct name is J. Donald Easton.
Upcoming Meetings

Feb. 16–Feb. 18, 2006
International Stroke Conference
Kissimmee, FL
http://strokeconference.americanheart.org/portal/strokeconference/sc/
Contact: strokeconference@heart.org

Feb. 20–Feb. 24, 2006
World Ophthalmology Congress
XXX International Congress of Ophthalmology
XVI Panamerican Congress of Ophthalmology
XVII Brazilian Congress of Prevention Blindness
Sao Paulo, Brazil
http://www.ophthalmology2006.com.br/
Contact: info@ophthalmology2006.com.br

Feb. 25–March 3, 2006
Tucson, AZ
http://www.nanosweb.org/meetings/nanos2006/
Contact: ekunsey@nanosweb.org

March 2–March 5, 2006
American Society of Neuroimaging Annual Meeting
San Diego, CA
http://aswnet.org
Contact: asn@llmsi.com

March 15–March 19, 2006
American Assn. of Pediatric Ophthalmology & Strabismus (AAPOS) Annual Meeting
Keystone, CO
http://www.aapos.org/2006+annual+meeting.htm
Contact: aapos@aao.org

April 1–April 8, 2006
58th Annual Meeting of the American Academy of Neurology (AAN)
San Diego, CA
http://am.am.com/
Contact: memberservices@aam.com

April 22–April 27, 2006
American Association of Neurological Surgeons Annual Meeting
San Francisco, CA
http://www.aans.org/annual/2006/default.asp
Contact: info@aans.org

April 29–May 5, 2006
44th Annual Meeting of the American Society of Neuroradiology (ASNR)
San Diego, CA
http://www.asnr.org/
Contact: vgeisendorfer@asnr.org

April 30–May 4, 2006
The Association for Research in Vision and Ophthalmology (ARVO)
Fort Lauderdale, FL
Contact: arvo@arvo.org

May 16–May 20, 2006
15th European Stroke Conference
Brussels, Belgium
http://www.eurostroke.org
Contact: Hennerici@eurostroke.org

May 21–May 23, 2006
Society of Neurological Surgeons Annual Meeting
Durham, NC
http://www.societyns.org/meeting/index.html

May 27–May 31, 2006
16th Meeting of the European Neurological Society
Lausanne, Switzerland
http://www.akm.ch/ens2006/
Contact: info@akm.ch

June 13–June 17, 2006
Canadian Congress of Neurological Sciences Annual Meeting
Montreal, Quebec
http://www.ccns.org/ccns_information/events/annual_meeting/prelim_progdraft.html
Contact: web@ccns.org

June 22–June 25, 2006
48th Annual Scientific Meeting of the American Headache Society
Los Angeles, CA
http://ahsnet.org/calendar/
Contact: alsmtgs@talley.com
July 2–July 8, 2006
11th International Congress on Neuromuscular Diseases
Istanbul, Turkey
http://www.icnmd2006istanbul.org
Contact: icnmd2006@flaptour.com.tr

July 8–July 12, 2006
5th Forum of European Neuroscience
Vienna, Austria
http://fens2006.neurosciences.asso.fr/
Contact: christiane.riedl@uibk.ac.at

July 12–July 15, 2006
17th International Perimetric Society Meeting
Portland, OR
http://webeye.ophth.uiowa.edu/ips/meetings.htm
Contact: cajohnso@discoveriesinsight.org

Sept. 1–Sept. 6, 2006
10th Congress of the European Federation of Neurological Societies
Glasgow, UK
http://www.kenes.com/efns2006/
Contact: efns06@kenes.com

Sept. 9–Sept. 16, 2006
XVIth International Congress of Neuropathology
San Francisco, CA
http://www.icn2006.org/

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

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

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

36th Annual Meeting of the Society for Neuroscience
New Orleans, LA
http://web.sf.n.org
Contact: info@sf.n.org

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

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

Nov. 11–Nov. 14, 2006
Annual Meeting of the American Academy of Ophthalmology (AAO)
Los Vegas, NV
http://www.aa.org/aa/annual_meeting
Contact: meetings@aa.org

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

Feb. 10–Feb. 15, 2007
Snowbird, UT
http://www.nanosweb.org/meetings/index.htm
Contact: info@nanosnet.org
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