JOURNAL OF Neuro-Ophthalmology
The Official Journal of the North American Neuro-Ophthalmology Society

VOLUME 18, NUMBER 1, MARCH 1998

Contents

1 Ocular Neuromyotonia: Three Case Reports With Eye Movement Recordings
Robert D. Yee and Valerie A. Purvin

9 Foveal Cone Dysfunction Syndrome
Martin W. ten Hove, R. Michael Siatkowski, and J. Lawton Smith

15 Occult Maculopathy and the Focal ERG
Michael L. Slavin

17 The Treatment of Periocular and Facial Pain With Topical Capsaicin
Norah S. Lincoff, Pamela P. Rath, and Michio Hirano

21 Follow-up Studies on Pattern Reversal Visually Evoked Cortical Potentials in a 2-Year-Old Child with Optic Neuritis
Kimi Sato, Emiko Adachi-Usami, and Atsushi Mizota

25 Steroid-Responsive HIV Optic Neuropathy
Ben J. L. Burton, Alex P. Leff, and Gordon T. Plant

30 Late-Onset Leber’s Hereditary Optic Neuropathy
E. Todd Ajax and Randy Kardon

32 Presumed Bilateral Occipital Neurosarcoidosis: A Case Report
Syndee J. Givre and Joel S. Mindel

36 A New Clinical Technique for Demonstrating Changes in Eye Acceleration During Horizontal Saccades in Patients With Partial Internuclear Ophthalmoplegias
Peter Brown

(continued on next page)
Contents (continued)

40 Ocular Tilt Reaction With Vertical Eye Movement Palsy Caused by Localized Unilateral Midbrain Lesion
Tsutomu Ohashi, Kikuro Fukushima, Shinki Chin, Takayuki Harada, Kazuhiko Yoshida, Minoru Akino, and Hidehiko Matsuda

43 Saccadic Ping-Pong Gaze
Ken Johkura, Atsushi Komiyama, Mari Tobita, and Osamu Hasegawa

47 Terminating Attacks of Ocular Neuromyotonia
Avinoam B. Safran and Michel Magistris

49 Papilledema in a Man With an “Occult” Dural Arteriovenous Malformation
Timothy J. Martin, D. Antonio Bell, and John A. Wilson

53 Pseudotumor Cerebri Sine Papilledema with Unilateral Sixth Nerve Palsy
Rohit Krishna, Gregory S. Kosmorsky, and Kenneth W. Wright

56 Bilateral Anterior Ischemic Optic Neuropathy Following Influenza Vaccination
Aki Kawasaki, Valerie A. Parvin, and Rosa Tang

60 Optic Nerve Head Swelling in the Hadju-Cheney Syndrome
Karl C. Golnik and Robert C. Kersten

66 Literature Abstracts—Europe
H. Esriel Killer

Larry P. Frohman and Paul Lama

Lippincott-Raven Publishers cannot be held responsible for errors or for any consequences arising from the use of the information contained in this journal. The appearance of advertising in this journal does not constitute an endorsement or approval by Lippincott-Raven Publishers of the quality or value of the product advertised or of the claims made for it by its manufacturer.

PERMISSION TO PHOTOCOPY ARTICLES: This publication is protected by copyright. Permission to photocopy must be secured in writing from: Permissions Dept., Lippincott-Raven Publishers, 227 East Washington Square, Philadelphia, PA 19106-3780; FAX: 215-238-4419; or Copyright Clearance Center (CCC), 222 Rosewood Dr., Danvers, MA 01923; FAX: 508-750-4470; or UMI, Box 49, 300 North Zeeb Road, Ann Arbor, MI 48106-1346; FAX: 313-761-1203.

Manuscripts should be submitted to Ronald M. Burde, M.D., Professor of Ophthalmology/Neurology/Neurosurgery, Albert Einstein College of Medicine, 131 East 210th Street, Bronx, New York 10467.

Address for subscription information, orders, or changes of address (except Japan): 12107 Insurance Way, Hagerstown, MD 21740, or call 1-800-638-3030; in Maryland call collect 301-761-2300. Subscribers requiring an address change must submit an old mailing label and their new address, including the zip code. No claims for copies lost in the mail can be allowed unless they are received within 90 days of the date of issue. Claims for issues lost as a result of insufficient notice of change of address will not be honored.

Advertising inquiries should be directed to Christa Deeden, Lippincott-Raven Publishers, 227 East Washington Square, Philadelphia, PA 19106-3780. Phone: (215) 413-4074; Fax: (215) 238-4461.
Ocular Neuromyotonia: Three Case Reports With Eye Movement Recordings

Robert D. Yee, M.D., F.A.C.S., and Valerie A. Purvin, M.D.

The objective of this article was to evaluate the etiologies, findings, and treatment of ocular neuromyotonia (ONM) in three case reports. The etiologies of ONM were determined by the histories, neuroradiologic tests, or biopsies. Clinical observations, videotaping, and electronic eye movement recordings documented the eye movement abnormalities. Intermittent diplopia developed several years after myelography with thorium dioxide (Thorotrast), radiation treatment for a pituitary tumor, and radiotherapy for medulloblastoma of the posterior fossa. All of the patients had intermittent, variable tropias that occurred spontaneously or were induced by eccentric gaze. One patient had a partial third nerve palsy, and another had a unilateral internuclear ophthalmoplegia (INO). ONM involved the paretic third nerve, extraocular muscles, and ipsilateral lateral rectus muscle in one patient, the paretic medial rectus muscle (INO) in one patient, a lateral rectus muscle (INO) in one patient, and a lateral rectus muscle in the last patient. Eye movement recordings were consistent with spasms of the involved muscles. Carbamazepine (Tegretol) abolished the ONM in two patients. The other patient had been taking carbamazepine for seizures and developed ONM when the dose was decreased. Increasing the dose abolished the ONM. ONM is an unusual cause of intermittent diplopia and strabismus, but its characteristic history and signs identify it easily. Damage to the peripheral cranial nerves might produce segmental demyelination, axonal hyperexcitability, and a self-perpetuating, reverberating circuit that causes spasms of the extraocular muscles.

Key Words: Ocular neuromyotonia—Eye movement recordings.

Ocular neuromyotonia (ONM) produces transient, involuntary spasm of an extraocular muscle, intermittent diplopia, and strabismus. Clark described the first patient with this disorder in 1966 (1), but Ricker and Mertens were the first to use the term “ocular neuromyotonia” in a second case report in 1970 (2). ONM typically begins months to years after radiotherapy for a tumor in the sellar and parasellar areas. It is a rare disorder that has been described infrequently (1-13). However, its characteristic clinical features are striking and, once recognized, readily lead to its diagnosis and an effective drug therapy. We describe three patients with ONM. These cases are unusual because of their documentation with eye movement recordings, the identification of thorium dioxide (Thorotrast) myelography as an etiology, the coexistence of internuclear ophthalmoplegia and ONM affecting the same extraocular muscle, and the likelihood that treatment with carbamazepine for seizures masked ONM until the dose was decreased.

METHODS

The patients were referred to the authors for neuroophthalmic consultations. Each patient gave their informed written consent to participate in the research protocol approved by the institutional review board for human subjects at the Indiana University School of Medicine. Videotaping and magnetic scleral search coils recorded the eye movements. The latter method has been described previously in detail (14,15). In brief, several turns of fine wire are embedded in an annulus made of soft contact lens material, which adheres tightly to the perilimbal sclera. The subject's head is centered in a cube made up of three sets of 6-foot diameter coils that induce a weak magnetic field within the cube. Rotation of the eyes and their contact lenses induce an electrical current that is amplified. The electronic and digital recording system can accurately record eye movements as small as 0.1 degree. The system's linear range is ±20 degrees horizontally and vertically, and its bandwidth is 0–100 Hz. The target is a bright red spot produced by a helium-neon laser. The laser light is reflected by a mirror galvanometer and is backprojected onto a translucent screen in front of the subject.

CASE REPORTS

Case 1

A 72-year-old man developed low back pain, weakness, and numbness of his legs 50 years ago. Forty years
ago, he had myelography with a contrast dye. Neither he nor his current physicians knew what dye had been used. Several months after his myelography, he had a severe infection. He did not recall the infection's location but remembered that he was treated with large doses of penicillin and streptomycin. Soon thereafter he had marked bilateral hearing loss. Over the ensuing years, he had six back surgeries for lumbar disk disease, but his back and leg symptoms slowly progressed. Several years ago, he developed incontinence of bladder and bowels. His physicians thought that he had a chronic mucocutaneous and a cauda equina syndrome caused by iophendylate.

Six years ago, he complained of episodes of intermittent diplopia that occurred several times each day and persisted for a few to many seconds. Three years ago, his ophthalmologist found limited abduction of the right eye and thought that he had a partial, right sixth nerve palsy. One year ago, the ophthalmologist detected pupillary dilatation, ptosis, and limitation of supraduction and infrafraction in the right eye, consistent with a right, partial, third nerve palsy. Neurologic examination showed moderately severe, bilateral leg weakness and loss of DTR's, proprioception and vibratory sensation in both legs. Perception of touch and pin also were decreased in both legs.

Neuro-ophthalmic examination showed 15 prism diopeters of right esotropia and 15 prism diopeters of right hypotropia in primary gaze. The right pupil was 6 mm in diameter and had decreased reactions to direct light stimulation and to near effort. The left pupil was 4 mm, and had normal reactions. There was 2–3 mm of right, upper lid ptosis. The range of eye movements in the left eye was full. In the right eye, abduction was decreased to 40 degrees, supraduction to 20 degrees, and infraduction to 20 degrees.

Gaze to the right for a few seconds caused a gradual increase in the right esotropia in primary gaze to 45 prism diopeters and the right hypotropia to 45 prism diopeters over a few seconds. After about 30 s, the right esotropia and right hypotropia gradually returned to their initial measurements over 10 s. A return to right gaze immediately afterward did not induce a similar, transient increase in strabismus. However, right gaze 2–3 min later did cause increased strabismus. During the transiently increased right esotropia, there was retraction of the right upper lid, but there was no change in the right pupil. Left gaze for a few seconds produced 20 prism diopeters of right esotropia in the primary position. The right esotropia persisted for ~15 s.

Magnetic search coil recordings showed only slightly decreased peak velocities of horizontal and vertical saccades in the right eye. In our laboratory, the mean peak velocity of 20 degrees, horizontal, and vertical saccades is ~400 ± 50 deg/s (±1 SD). The peak velocities of 20 degrees up and down saccades in the right eye were 360 and 320 deg/sec, respectively. In the left eye the velocities were 400 and 390 deg/sec for up and down saccades, respectively. Figure 1 shows vertical saccades for unpredictable target jumps across the center of the orbit.

Both eyes had postsaccadic drifts downward for 80 ms after most upward and downward saccades. The peak velocities of 20 degree right and left saccades were 380 and 370 deg/sec, respectively. Figure 2 shows horizontal saccades across center. Leftward saccades in the right eye have overshooting waveforms. After rightward saccades, both eyes show convergence movements. Figure 3 shows horizontal saccades during target jumps from center to left 15 degrees. After several seconds, the right eye has a decelerating intersaccadic drift toward the left (adduction) of initially 5 deg/sec and a progressive decrease in amplitudes of saccades.

Magnetic resonance imaging (MRI) of the spinal cord showed abnormal clumping and enhancement of the cauda equina. MRI of the head showed abnormal widening of the cerebral sulci, dilation of the lateral ventricles, old bilateral cortical infarcts, and extensive lesions in subcortical periventricular, brain stem, basal ganglia, and thalamic areas, consistent with ischemia. There was diffuse pial enhancement, sometimes nodular in pattern, throughout the cerebral cortex and prominently in the basilar cisterns. The enhancement also involved the structures in the pineal region and the superior vermis. Figure 4 shows abnormal pial enhancement along the right temporal lobe, extending to the right caverous sinus. The peripheral portion of the third nerve in the right cavernous sinus enhanced abnormally. A cisternal tap showed normal opening pressure, cytology, and chemistry of the cerebrospinal fluid (CSF). However, after the tap, the patient and his wife reported that his memory, alertness, and energy improved transiently, suggesting that he had normal pressure hydrocephalus.

A ventriculoperitoneal shunt was placed into the right lateral ventricle, and a biopsy of the leptomeninges and the right frontal cortex was performed. The biopsy showed thickening and fibrosis of the leptomeninges and gliosis of the cortical molecular layer and underlying white matter. There were small foci of mononuclear inflammatory cells in the leptomeninges, some of which contained brown pigment. The brown pigment was also free in the extracellular space. Iron and Fontana stains were negative. Transmission electron microscopy showed that the pigment was amorphous, dense osmiophilic granules in the cytoplasm of macrophages. The
osmiophilic granules were membrane bound. Scanning electron microscopy and x-ray energy dispersive analysis showed that the pigment was thorium. Figure 5 shows thorium's major peak at 2.996 KeV and its minor peak at 12.967 KeV. This finding proved that the myelographic contrast dye was thorium dioxide (Thorotrast). The patient developed a chronic, diffuse arachnoiditis, induced by this agent, that eventually produced a cauda equina syndrome, normal pressure hydrocephalus, a partial right third nerve palsy, and ONM. Chronic arachnoiditis or streptomycin might have caused the bilateral hearing loss.

The patient was treated with carbamazepine 200 mg orally twice daily. Within 1 day, the diplopia and ONM resolved. The ONM returned when the drug treatment was stopped 2 months later and resolved when the treatment was restarted.

Case 2
A 66-year-old woman had been diagnosed with a pituitary tumor and acromegaly 30 years ago. She underwent 19 radiation treatments and developed intermittent horizontal and occasionally vertical diplopia after the treatments. The episodes worsened over the past 5 months. They lasted several seconds and occurred many times each day. An MRI of the head showed an enlarged, empty sella with a small residual pituitary gland and a few lesions in the periventricular white matter of the cerebral hemispheres, consistent with ischemia. Proton and T2-weighted scans showed a small area of increased signal in the left medial longitudinal fasciculus in the pons. Results of magnetic resonance angiography were normal. She complained of imbalance while walking during the past year. Neurologic examination showed mild dysmetria on finger-to-nose testing and mild dysdiadochokinesia of the left arm and hand. Her gait had a normal base, but she could not walk in tandem.

Neuro-ophthalmic examination showed a left internuclear ophthalmoplegia (INO). The range of eye movements was full, except for limitation of abduction in the left eye to 40 degrees. Abducting nystagmus of the right eye was present in right gaze, and rightward saccades in the left eye were slow. Left gaze produced a mild, gaze-evoked nystagmus. Smooth pursuit was mildly impaired, and fixation did not normally suppress vestibular nystagmus induced by rotation of her chair.

There was no phoria in center gaze. Right gaze produced three prism diopters of exotropia, and left gaze eight prism diopters of esotropia. Several episodes of marked esotropia of the left eye were observed, as the right eye maintained fixation. They lasted 45–80 s. These episodes were induced by right gaze and up gaze, but sometimes occurred while fixation was maintained in primary gaze. No pupillary constriction was observed during the esotropia. Treatment with carbamazepine 200 mg orally twice daily was begun. The episodes of diplopia resolved within a few days.

Magnetic scleral search coil recordings were made while the patient was taking carbamazepine and 10 days after stopping the drug. During both sessions, marked slowing of rightward saccades in the left eye due to the left INO were found (Fig. 6). For example, the mean peak velocity of 20 degree rightward saccades in the right eye was 390 deg/s, but that of the rightward saccades in the left eye was only 110 deg/s. Leftward and vertical saccades in the left eye, as well as horizontal and vertical saccades in the right eye, had normal peak velocities. A small-amplitude (1 degree) right-beating, jerk nystagmus was found in primary gaze in the right eye, and a large-amplitude, ab-
ducting nystagmus of the right eye was present in right gaze.

No ONM was present during the session while carbamazepine was taken. After the medication was stopped, videotaping and search coil recordings documented the ONM. Episodes of esotropia occurred spontaneously during fixation in primary gaze and after return to primary gaze from right gaze and gaze up-and-right gaze. Their durations were 4–7 s, peak velocities 5–9 deg/s, and amplitudes 4–9 degrees. In Fig. 6, the left eye is covered, and the right eye is fixing the target. After return to primary gaze from right gaze, a left esotropia developed, lasting 7 s. The amplitude and duration of the left medial rectus spasms had been much greater before carbamazepine was initially given.

Case 3
A 47-year-old man developed imbalance and vertigo 5 years ago. A partial excision of a cerebellar medulloblastoma was performed, and he received radiotherapy and chemotherapy. Three years ago, he had grand mal seizures and was placed on carbamazepine 200 mg orally four times daily because of an allergic reaction to diphenylhydantoin. He had no subsequent seizures. The dose was decreased to 200 mg three times daily 1 year ago because of a mild decrease in the white blood cell count. He began to have episodes of intermittent binocular, horizontal diplopia 3 months ago. The episodes were often brought on by turning of his head to the left, but also occurred without a head turn or conscious change of gaze. They occurred three times to several times each day and persisted for 5 s to 20 min. MRI studies of the head had been performed every 6 months and showed no signs of recurrence of the tumor. His general neurologic examination was normal, except for mild gait ataxia.

Neuro-ophthalmic examination showed a left naso-temporal deviation of right esotropia in center gaze. The right eye was 10 prism diopters of right exotropia that persisted for 10–20 s. Magnetic scleral search coil recordings showed the right exotropia on return to primary gaze from right gaze. After 10–15 s there was a very low velocity, leftward drift of the right eye to the primary position as the right exotropia decreased. The range of eye movements were full in both eyes. The peak velocities of horizontal and vertical reflex saccades were symmetrical between both eyes and within the normal limits for our laboratory. The remainder of the eye movement recordings was also normal, except for a mild symmetrical decrease in horizontal pursuit gain. A complete blood count and platelet count were normal while the patient was taking carbamazepine 200 mg orally three times daily, and the blood level was 9.5 µm/ml (therapeutic range for epilepsy, 4–12 µm/ml). The episodes of ONM ceased after the dose was increased to 200 mg orally four times daily. His blood tests have remained normal and/or in the therapeutic range.

DISCUSSION

Differential Diagnosis
Many disorders cause intermittent diplopia and strabismus. Those that produce diplopia and strabismus in primary gaze include decompensated phorias, convergence spasm, myasthenia gravis, restrictive orbitopathies (Graves' ophthalmopathy), superior oblique myokymia, and congenital oculomotor palsy with cyclic spasms. Diplopia and strabismus occurring only in eccentric gaze are created by ocular myopathies (myasthenia gravis), cranial nerve palsies, restrictive orbitopathies, and INO.

ONM is a rare cause of intermittent diplopia and strabismus. Only 26 patients, including ours, have been described in the literature (1–13). However, the clinical history and the examination of ocular motility are distinctive. Because many patients with ONM have had radiotherapy for pituitary tumors, the onset of diplopia and strabismus suggests that there might be recurrence of the tumor with cranial nerve palsies. Recognizing the distinctive features of ONM can reassure the clinician and patient that a tumor has not recurred.
Extraocular muscle spasm occurs in other disorders, but these can be readily differentiated from ONM. In cyclic oculomotor palsy, the paralysed muscles have periods of spasm. However, the underlying extraocular muscle paresis persists between episodes, producing limitation of ductions and slowing of saccades. In addition, the oculomotor palsy is usually congenital. The ages of onset of reported cases of ONM range from 6 to 74 years, but the majority of patients are adults. In each instance, ONM was an acquired disorder. Superior oblique myokymia causes diplopia and monocular oscillopera. There are tonic, large-amplitude contractions of the superior oblique, as well as high-frequency, small-amplitude contractions of the muscle. Although ONM has involved the superior oblique muscle in several patients, none of them have had monocular, torsional oscillations. Convergence spasm produces intermittent esotropia and diplopia. However, the other components of the near reflex (miosis and accommodation) are usually present.

Gaze-Induced and Spontaneous ONM

In ONM, intermittent spasms of extraocular muscles create strabismus and diplopia in primary gaze. Eccentric gaze often induces spasm of an agonist muscle that persists on return to primary gaze. For example, in case 1, left gaze produced spasm of the right medial rectus and right inferior rectus so that the right esotropia and right hypotropia increased on return to primary gaze. Right gaze caused spasm of the right lateral rectus and a right exotropia in primary gaze. In case 2, right gaze and upward gaze produced left medial rectus spasm and left esotropia in primary gaze. In case 3, right gaze caused spasm of the right lateral rectus and right exotropia on return to primary gaze.

The effects of eccentric gaze were documented in 24 of the 26 reported cases. Eccentric gaze evoked extraocular muscle spasms in 17 of the 24 patients. It was necessary to maintain eccentric gaze for several seconds to a few minutes. ONM will be missed if prolonged periods of eccentric gaze are not used. In case 1 periodic volitional saccades into left gaze every 1.5 seconds also were sufficient to induce extraocular muscle spasms. In this patient, a refractory period was found after an episode of gaze-induced ONM. Return to right gaze did not induce another episode of ONM for 2-3 min. Helmchen and colleagues used electro-oculography to record ONM of the left lateral rectus in a patient (8). Repetitive saccades into left gaze also induced episodes of ONM. The authors documented whether or not the spasms occurred spontaneously in primary gaze without prior eccentric gaze in 18 patients. Spasms were spontaneous in 15 patients, including case 2.

The patient's history sometimes indicates that the ONM is gaze induced. For example, patient 3 reported that diplopia occurred after head turn to the left that induces gaze toward the right and activation of the affected right medial rectus muscle. However, the history alone cannot differentiate gaze-induced from spontaneous ONM, because the patient might not be aware that a reflex or voluntary change in gaze precedes the diplopia. Therefore, the clinician must observe the eyes in primary gaze and after many seconds of eccentric gaze.

Spasm of Extraocular Muscles

Versus Ophthalmoplegia

Detailed examination shows that the strabismus in ONM results from extraocular muscle spasm rather than from extraocular muscle paresis. In the reported cases, the spasms and deviations persisted for several seconds to a few minutes. Every extraocular muscle, except the inferior oblique, has been affected in ONM. In the 26 reported cases, the medial rectus was involved in 13, superior rectus in five, inferior rectus in five, lid levator in five, lateral rectus in 11, and superior oblique in six. The iris sphincter muscle was affected in two patients (5,13). ONM has been unilateral in every patient, except for bilateral involvement of third nerve, extraocular muscles in one patient (12).

Extraocular muscle spasm in ONM can be distinguished from paresis resulting from a cranial nerve palsy. Slowing of saccades in ONM is usually slight, but the decrease in peak saccadic velocity is marked in cranial nerve palsies. Right sixth and third cranial nerve palsies were thought to be present in case 1 because of the limitation of eye movements. However, the electronic eye movement recordings indicated that the limitations of abduction, supraduction, and infraction in the right eye were probably caused by cocontraction of antagonist muscles. The peak velocities of horizontal and vertical
saccades in the right eye were only slightly decreased, compared with the velocities of saccades in the left eye. These findings can be explained by the lack of inhibition of antagonist muscles and a slight decrease in force generated by agonist muscles that are tonically contracted (spasm). Extraocular muscle paresis would cause much larger decreases in peak velocities.

Frohman and Zee (11) recorded eye movements in a patient with ONM of the inferior rectus, superior rectus, and medial rectus muscles of the right eye. After sustained left gaze, post-saccadic drift to the left at the end of leftward saccades increased, and the peak velocities of leftward saccades decreased slightly in the right eye. These changes were consistent with tonic contraction of the right medial rectus. The baseline right esotropia and right hypertropia in primary gaze in case 1 were probably also produced by tonic spasms of the right medial rectus and right inferior rectus. Morrow et al. (12) recorded saccades and found slowing in all directions in a patient with bilateral ONM involving muscles innervated by the third nerve. They attributed the slowing to impaired plastic firing of agonist muscles and tonic contraction of antagonist muscles. Between episodes of ONM, the peak velocity of saccades was only slightly decreased. ONM and cranial nerve palsy can affect the same extraocular muscles (5,6,13) (case 1), and aberrant regeneration of the third nerve can also be present (5,13). However, a peripheral nerve that is damaged enough to markedly decrease saccadic velocities might not be able to demonstrate ONM.

In case 2 the peak velocities of leftward saccades in the left eye were markedly slow because of the left INO. This is the first reported association of ONM and INO. In addition, the patient had other eye movement abnormalities (gaze-evoked nystagmus in left gaze, impaired smooth pursuit and impaired suppression of vestibulo-ocular responses by fixation) found with disorders of the cerebellum and brain stem. The left MLF lesion found on MRI and the left INO could have been caused by ischemia secondary to the radiotherapy. However, the INO and other eye movement abnormalities do not contribute to the ONM. The MLF lesion blocks the normal recruitment of oculomotor neurons during conjugate, versional eye movements but does not damage the motor neurons or their axons. Thus, the latter can participate in the phenomenon of ONM. In case 3 the peak velocities of saccades were normal. Among our cases, the ONM was least severe in this patient, probably because carbamazepine was ameliorating some of its effects when the eye movement testing was performed.

Saccadic velocities can be normal in ophthalmoplegia caused by myasthenia gravis and restrictive ophthalmopathies, such as Graves’ ophthalmopathy. However, patients with ONM do not have the other associated ocular and systemic signs of these disorders.

Causes of ONM

In 16 of the 26 cases of ONM, radiotherapy had been given for a tumor in or around the sella. The tumors included pituitary adenomas, cranioopharynigomas, an ethmoid carcinoma, a thalamic glioma, a chondrosarcoma, and a rhabdomyosarcoma. The total radiation doses ranged from 20 to 77 Gy, and the symptoms of ONM began several months to 17 years later. Patient 2 had undergone radiotherapy for a pituitary adenoma and acromegaly 30 years earlier. Patient 3 had undergone radiation treatment to the posterior fossa for a cerebellar medulloblastoma, but the sellar area probably also received radiation. Ten previously reported patients did not have radiation to the sellar and parasellar areas. Two of these patients had compressive lesions, including a clivus chordoma (4) and a supraclinoid carotid artery aneurysm (13). One patient had a radical mastectomy and local irradiation for breast adenocarcinoma without evidence of metastasis by CSP examination or computed tomography (5). The seven remaining patients had no known disorder, that might have been associated with ONM. In case 2 of these patients, alcohol ingestion induced ONM (13). Shults et al. stated briefly that one of them had examined four other patients with ONM involving the third nerve (three postradiation for tumors, one idiopathic) and that they believed another patient described by other investigators had ONM of the third nerve caused by a supraclinoid aneurysm (5,16).

Case 1 is unique because chronic arachnoiditis caused by thorium dioxide myelography is the most likely etiology of the ONM. Thorium dioxide was used as an x-ray contrast dye from 1928 to the mid-1950s in Europe and the United States (17-19). Thorotrast was a 25% colloidal suspension of thorium dioxide. It was used for angiography and to fill body cavities. Neuroradiologic applications included cerebral angiography, ventriculography, myelography, and opacification of brain abscesses. Unfortunately, severe complications, including malignancies, were not identified until 1947 (20). After administration, thorium dioxide is preferentially stored in reticuloendothelial cells in the liver, spleen, bone marrow, and lymph nodes. Malignant tumors of the liver, leukemias, blood dyscrasias, and asplenism have been reported after thorium dioxide injection. Extravasated material around the injection site produced chronic, inflammatory granulomas (thorotromas), especially in the neck when the dye was used for cerebral angiography.

Thorium 232 is a radioactive alpha emitter that has a physical half-life of 1.39 × 10^10 years and a biologic half-life of 400 years (21). Each gram of thorium delivers about 890 cGy to the body each year. Its radioactive daughters are beta and alpha emitters, which deliver another 890 cGy each year. Secondary neoplasia and chronic inflammation are probably due to radiation. Injection of thorium dioxide into brain abscesses and into a subdural hematoma has caused local granulomas, a gliosarcoma, and a meningioma (22-24). Myelography has produced a meningioma, a Schwannoma, chronic arachnoiditis, and a cauda equina syndrome (25-30). The patient described by Kaplan et al. (26) had severe, diffuse arachnoiditis, multiple cranial nerve palsies, right
optic atrophy, bilateral neurosensory hearing loss, a cauda equina syndrome, and “external ophthalmoplegia.” Our patient and his current physicians suspected that ipophendylate (Pantopaque) had been used for his myelography 40 years ago. This material can also cause chronic arachnoiditis (31–33). However, scanning electromyography and x-ray energy dispersive analysis definitively showed that thorium dioxide had actually been used.

Mechanism of ONM

Myotonia is an abnormal delay in relaxation of muscle fibers caused by disorders of the muscle membrane. Neuromyotonia is a delayed muscle relaxation caused by repetitive firing in peripheral nerves triggered by an impulse. Disorders that damage peripheral nerves have caused neuromyotonia in limb muscles. Interestingly, these disorders include peripheral neuropathy, traumatic peripheral neuropathy, and radiation-induced damage to the brachial plexus (34–38). Histopathologic examination of peripheral nerves in these disorders have shown segmental demyelination, degeneration of axons, axonal sprouting, and remyelination. Electromyography of limb muscles have shown continuous motor unit firing, fibrillations, fasciculations, and myokymia. Hemifacial spasm might be caused by compression of the peripheral facial nerve at its root entry zone in the brain stem (39,40).

The mechanism of ONM might be similar. For example, Ricker and Mertens (2) and Papst (3) found abnormalities in electromyography of extraocular muscles between episodes of ONM, that they interpreted as neurogenic in origin. Many cases of ONM followed radiation for tumors in the sellar and parasellar areas. This observation suggests that damage to the peripheral nerves in or near the cavernous sinus sets the stage for ONM. The patient described by Ricker and Mertens (2) and our case 1 had ONM of muscles innervated by ipsilateral sixth and third cranial nerves, suggesting that these nerves had been damaged in or near the cavernous sinus. The patient described by Helmlchen et al. (8) and case 1 had ONM of the lateral rectus and ipsilateral, partial third nerve palsies. MRI in case 1 demonstrated a third nerve lesion in the cavernous sinus.

Ephaptic transmission (axon-to-axon crosstalk) has been proposed as a mechanism in limb neuromyotonia, ONM, hemifacial spasm, and the misdirection syndrome of third nerve palsy (39–42). In a previously damaged part of the peripheral nerve, neural signals transmitted through axons that are demyelinated and hyperexcitable might spread to adjacent axons. The extraocular muscle spasm in ONM persists for many seconds even when a change of gaze would not normally excite the involved muscles. A self-perpetuating, reverberating circuit in which axons are reinnervated might sustain the contraction. Other explanations for these phenomena have been proposed, including reorganization of neurons in the brain stem nuclei secondary to retrograde degeneration, ephaptic transmission in the nuclei, and reorganization of patterns of motor output in the nuclei (42–44).

Treatment

Of the 26 documented cases of ONM, only one patient experienced spontaneous resolution (9). Sixteen patients were treated with carbamazepine. The ONM resolved or significantly decreased with treatment in 14 of these patients. In most patients, dosages of carbamazepine of 200 mg twice daily to 200 mg three times daily were effective. The treatment for one patient was stopped after 1 month, but the ONM did not recur. Carbamazepine was not effective in one patient and was not tolerated by another patient. Phenytoin and clonazepam were used for a few patients but were not effective. The effectiveness of carbamazepine is interesting in terms of the possible mechanism of ONM because it stabilizes cell membranes. Case 3 is unique in that carbamazepine had been given before the onset of ONM. Because the diplopia did not occur until the dose was decreased, it is likely that the medication had masked the manifestations of ONM.

Acknowledgment: This research was supported in part by an unrestricted Development Grant to the Indiana University Department of Ophthalmology (to R.D.Y.) from Research to Prevent Blindness, Inc., New York, New York.

REFERENCES

Foveal Cone Dysfunction Syndrome

Martin W. ten Hove, R. Michael Siatkowski, and J. Lawton Smith

Summary: Our objective was to describe and expand the clinical spectrum of a rarely detected, previously reported photoreceptor disorder restricted to the foveal cones. Three patients with bilaterally decreased acuity and hemeralopia were examined to exclude a structural, vascular, inflammatory, or degenerative process. Each patient underwent a full neuroophthalmic examination, including full-field and focal cone electroretinogram (ERG). All three patients had normal-appearing fundi, mild dyschromatopsia, central or paracentral visual field depressions, normal full-field photopic and scotopic ERGs, and markedly reduced focal, foveal cone ERG responses. One patient had a ring atrophy and an asymptomatic family member with abnormal full-field and focal cone ERG responses. The syndrome of acquired foveal cone dysfunction presents as a bilateral, painless, progressive central visual loss with minimal or absent fundus changes. It eludes diagnosis until focal, foveal cone ERG is performed.

Key Words: Foveal cone—Photoreceptor disorders.

Cone dysfunction is an often unrecognized cause of visual loss later in life (1). Such patients present with decreased central acuity, hemeralopia, and/or dyschromatopsia (2,3). Fundus abnormalities are typically subtle; however, a number of cases with bulb's eye macular changes and temporal atrophy of the optic disk have been described (1–3). Electroretinography (ERG) establishes the diagnosis by demonstrating abnormal cone and normal rod responses (2,3). Isolated involvement of the macular cones may represent a forme fruste of panretinal cone dystrophy or, alternatively, may be a separate disease entity. Patients with this condition also present with decreased acuity and/or hemeralopia. However, there are sufficient numbers of intact peripheral cones to allow at least partial preservation of color discrimination. Matthews et al. have observed five patients with negative family histories of eye disease who had subnormal focal (foveal) ERG amplitudes and normal full-field ERG responses (4). We present three similar cases that add to the understanding and awareness of this entity.

PATIENTS AND METHODS

Three patients (53, 58, 72 years of age) with decreased visual acuity and hemeralopia were seen at the Bascom Palmer Eye Institute between 1989 and 1994. Each patient underwent full neuroophthalmic examinations, including Goldmann perimetry, Farnsworth D-15 and Ishihara color vision testing, fundus photography, fluorescein angiography, and full-field ERG. Focal cone ERG testing was performed by Dr. Eliot L. Berson and Dr. Ronald E. Carr.

Full-field ERGs were recorded using International Society for Clinical Electrophysiology of Vision (ISCEV) standard techniques under scotopic and photopic conditions. Focal cone ERGs were performed in dim illumination under maximal mydriasis. A corneal bipolar-electrode contact lens and forehead ground electrode were used. The fellow eye was patched. A hand-held stimulator-ophthalmoscope projected the central 4 degrees with a repetitive white stimulus lasting 12 ms, whereas the surrounding 10 degrees received a steady white light to minimize the effects of stray light from the central stimulus. Flickering central stimuli were used. The signal was amplified by 10,000 times, attenuated with respect to line noise (60-Hz notch filter), and amplified again by spike filters tuned to 10 Hz, 25 Hz, 42 Hz and 50 Hz (stimulus frequencies). Wave forms were analyzed for peak-to-peak b-wave amplitude and implicit time.

CASE REPORTS

Case 1

A 58-year-old woman presented with impairment of vision in daylight for the preceding 2 years. Vision had declined from 20/20 in both eyes to 20/50 in the right eye and 20/40 in the left eye. She described bothersome "glare" with daylight illumination, and commented, "Like a cat, I see better at night." Cataract extraction in the right eye was performed for a mild lens opacity, which was originally felt to be the cause of her poor acuity. However, postoperatively, acuities gradually decreased further over 1 year to 20/140 in the right eye and 20/50 in the left eye. Therapeutic trials of oral prednisone and vitamin B12 injections offered no improvement.

Past medical history was notable for "migrainous" headaches, hypertension, recurrent depression, and alcohol abuse. She was on no medications other than Ten-
ormin. Family history was significant for glaucoma and cancer.

Best corrected visual acuity was 20/140 in both eyes, improving with pinhole to 20/120 in the right eye and 20/80 in the left eye. Six of 10 presented Ishihara color plates were correctly identified in each eye. Pupils were equal and briskly reactive without an afferent defect. Peripheral fields were full, but central fields showed bilateral cecocentral scotomas that were larger for color targets than for white targets. Slit-lamp examination showed pseudophakia in the right eye and pseudoxfoliation in the left eye. The fundi were normal apart from mild temporal disk pallor (Fig. 1).

Serologic tests for syphilis, Lyme disease, and thyroid dysfunction were all normal. Full-field ERG was within normal limits (Fig. 2). Focal ERG performed by Dr. Berson showed bilaterally reduced (0.11 μV in the right eye and 0.12 μV in the left eye; normal, 0.18–0.56 μV) and delayed responses (45 ms in the right eye and 44 ms in the left eye; normal, < 38 ms).

Case 2

A 72-year-old man presented with difficulty reading and discriminating colors for 3 years. Vitamin A, B12, and E replacement did not improve visual function. Past medical history was remarkable for diabetes mellitus for 8 years and a remote history of bilateral Bell's palsies. There was no family history of visual loss.

Best corrected visual acuity in both light and dark illumination was 20/100 in the right eye and 20/140 in the left eye. Farnsworth color testing suggested a deuteranopic axis of confusion. Pupils were 2 mm in diameter and minimally reactive without an afferent defect. Peripheral fields were full, but central fields showed large central scotomas. Slit-lamp examination showed only mild nuclear sclerosis bilaterally. Fundi were both normal, although the foveal reflexes were somewhat blunted.

MRI of the brain showed only moderate cerebral atrophy. Vitamin A, B12, and E levels were normal. A Lyme disease panel, rapid plasma reagin (RPR), fluorescent treponemal antibody-absorption (FTA-ABS), and retinal S antigen were all negative. Cerebral angiography was unremarkable. Full-field ERG responses were within normal limits. The patient was referred to Dr. Ronald Carr for foveal ERG testing, which showed reduced and delayed responses (Fig. 3).

Case 3

A 53-year-old woman complained of bilateral, painless, progressive visual loss since 40 years of age. By old records, visual acuity had declined from 20/30+ in each eye to the 20/60–20/70 level. Past medical history was significant for migraine headaches, temporomandibular joint syndrome, and depression. She was taking Cafergot (Sandoz Pharmaceutical Corp, East Hanover, NJ), Midrin (Carrick Laboratories, Inc., Cedar Knolls, NJ), and Prozac (Eli Lilly, Indianapolis, IN).

Best corrected visual acuities in normal illumination were 20/200 in the right eye and 20/400 in the left eye, improving to 20/60–2 in the right eye and 20/60 in the left eye in dim illumination. With pinhole use, acuities improved further to 20/30 in the right eye and 20/40 in the left eye. Ishihara color plates were correctly identified seven and eight times (out of 15) in the right and left eyes, respectively. Farnsworth D-15 test was normal in both eyes. Pupils were briskly reactive without afferent defect. On Aimark perimetry and tangent screen, peripheral fields were full with bilateral cecocentral scotomas associated with ring scotomas (Fig. 4). Slit-lamp examination was unremarkable. The fundi were normal except from a mildly blunted foveal reflex on the right. Full-field ERG responses were within normal limits. Visual evoked potentials, optic nerve ultrasonography, carotid ultrasound, magnetic resonance imaging of the brain, and Holter monitoring were all normal. She was referred to Dr. Ronald Carr for foveal cone ERG testing, which was abnormal at all frequencies (Fig. 5). The patient's daughter, who was asymptomatic with 20/20 vision in both eyes, was also tested and had full-field and foveal cone ERG responses at the lower limit of normal.

FIG. 1. Case 1. Fundi showing mild disk pallor in both eyes (arrows) and normal maculae. A: Right eye. B: Left eye.
FOVEAL CONE DYSFUNCTION SYNDROME

11

Rod ERG b-wave
Mixed cone-rod ERG b-wave
a-wave
a-wave
Cone ERG b-wave
a-wave
Cone flicker
Amplitude (uv)
OD / OS
Rod ERG b-wave
232.4 / 187.5
Mixed cone-rod ERG b-wave
494.4 / 455.3
a-wave
318.4 / 365.6
a-wave
48.4 / 41.0
Cone ERG b-wave
48.4 / 41.0
a-wave
9.76 / 7.69
Cone flicker
53.3 / 46.0
Implicit time (ms)
OD / OS
Rod ERG b-wave
48.0 / 41.2
Mixed cone-rod ERG b-wave
50.2 / 50.4
a-wave
16.4 / 16.4
a-wave
17.6 / 17.6
Cone ERG b-wave
13.6 / 33.0
a-wave
17.6 / 17.6
Cone flicker
26.5 / 30.4

FIG. 2. Case 1. A: Full-field ERG with normal amplitudes and implicit times. Tracings (top to bottom) are as follows: rod ERG, mixed cone-rod ERG, cone ERG, and cone flicker. B: Table shows absolute values of amplitude and implicit times.

DISCUSSION

Acquired generalized cone dysfunction generally presents early in life, but occasionally as late as the sixth decade of life (1). Both sporadic and hereditary forms have been reported (2), the majority of the latter transmitted as an autosomal-dominant trait (3). Although acquired, generalized cone dysfunction affects all of the retina's 5-7 million cones, it is the involvement of the 0.44 million cones subserving the central 10 degrees that results in impaired acuity (5). Isolated involvement of the central foveal cones would allow peripheral cone function with seemingly normal color discrimination. Whether isolated foveal cone dysfunction represents a unique

FIG. 3. Case 2. A: Normal full-field ERG. B: Table of amplitudes and implicit times. C: Focal cone ERG shows subnormal amplitudes at all temporal frequencies.

entity or an earlier, incomplete stage of a generalized cone disorder is unknown. Indeed, whether this entity is limited to the cone photoreceptors in this area is also undetermined.

Symptomatic central visual loss in generalized cone dystrophy may progress for years before stabilizing, similar to the duration of progression observed in our cases (2–13 years) and those of Matthews et al. (1–10 years) (4). Reliance on rod photoreceptors can cause patients to complain of daytime “glare” or hemeralopia. Hemeralopia is readily distinguished from other causes of daytime glare (e.g., cataract) through proper dilated slit-lamp examination. A pinhole apparatus may improve acuities recorded under bright illumination even beyond the best refraction, presumably by decreasing the amount of light reaching the retina (6). Difficulty with color vision and visual field loss also may be presenting symptoms.

Field defects in generalized cone dysfunction syndromes include enlarged blind spots and ring scotomas, as well as centrocecal, central, and paracentral scotomas (2,6). However, in the series of focal, foveal cone syndromes described by Matthews et al. (4) and Miyake et al. (7), only central and paracentral scotomas were noted. In Krill’s series of 45 generalized cone dystrophies, he noted ring scotomas to be associated with bull’s eye type changes in the macula (2). In our case 3, although the maculae were normal, a ring scotoma was evident, extending from 20 to 35 degrees when measured with a white stimulus, an area densely populated by rod photoreceptors. This implies that central rods also may be impaired in this disease process or that larger numbers of peripheral cones may be present in some individuals. One must remember that the extent of such field defects vary with background illumination and target luminance. Automated perimetry of the central 24 or 30 degrees may miss ring scotomas, which may only be appreciated with the amplification achieved by tangent field and kinetic perimetry. Alternatively, the field defect may be outlined with the use of focal ERG testing as suggested by Matthews (4) and is the only pure way to determine the exact extent and density of the field deficit.

Color vision in isolated foveal cone dysfunction may depend on stimulus size and the topographic extent of cone involvement. Two of our cases had only minimally impaired color vision based on Farnsworth D-15 and Ishihara plate testing. Our case 2 (a man) had a red-green defect similar to that in two cases described by Matthews.
Focal ERG OD
Case 3

FIG. 5. A: Normal full-field ERG. B: Table of amplitudes and implicit times. C: Focal cone ERG shows subnormal amplitudes at all temporal frequencies.

et al. (4), as did all three cases reported by Miyake et al. (7). This is a violation of Kollner's rule (that retinal conditions cause blue-yellow defects); however, in our case a preexisting dyschromatopsia could not be ruled out.

Late-onset acquired generalized cone dysfunction with abnormal full-field ERG has been well described (2,8,9). The percentage of cases with a positive family history is inversely proportional to age at presentation. None of our cases of focal, foveal cone dysfunction had a positive family history; however, the asymptomatic daughter of case 3, who simply accompanied her mother to her examination, was found to have focal and full-field cone ERG amplitudes at the lower limit of normal. Miyake et al. (7) reported three family members who noted decreased central vision at 13, 29, and 35 years of age and were subsequently shown to have abnormal focal ERG and yet normal full-field ERG. He also demonstrated that as the focal ERG spot size increased (from 5 to 15 degrees), the ERG amplitude increased, supporting the notion that central cones are the ones most impaired.

Progression of both visual loss and full-field ERG changes has been reported with acquired generalized cone dysfunction (10); however, electrophysiologic evidence that macular cones are the first to be involved, with subsequent spread to the peripheral cones, is still lacking.

Focal ERG abnormalities in patients with normal full-field ERGs are also seen in Stargardt's disease, juvenile macular dystrophy, age-related macular degeneration, and macular scars (11,12). These conditions are readily differentiated from foveal cone dysfunction by their ophthalmoscopic appearance. Cancer-associated retinopathy may present similarly (and was tested for in case 2); however, it can be distinguished by its rapidly progressive course (13). Impaired vision secondary to optic atrophy or amblyopia can be excluded because focal ERG is normal in these disorders (12).

Optic atrophy, when it occurred in our cases, was very subtle. The exact mechanism for its development is unknown. Primary foveal photoreceptor dysfunction may lead to subsequent bipolar and ganglion cell dysfunction,
resulting in optic disk pallor; optic atrophy is frequently seen in retinitis pigmentosa and other retinal dystrophies and degenerations. Conversely, long-standing optic neuropathies (e.g., glaucoma) may result in b-wave changes on full-field ERG; in these cases, retrograde degeneration of mid-retinal structures may have occurred over time. Nevertheless, in our patients, the presence of minimal optic atrophy, obvious focal ERG abnormalities, and hemeralopia all indicate that the primary site of pathology is the retina rather than the optic nerve.

The search for the etiology of central visual loss in patients with foveal cone dysfunction may lead to numerous unnecessary investigations, including magnetic resonance imaging (MRI), computed tomography (CT) (4), lumbar puncture, psychiatric assessments (4), and expensive laboratory workups. Patients with acquired cone dysfunction presenting in later adulthood may be particularly difficult to diagnose, especially if the family history is negative. Recognition of this entity may avoid unnecessary, expensive diagnostic testing and enable clinicians to properly counsel such patients. Although the cost of the equipment necessary to perform focal ERG is high (approximately $25,000–30,000), in the long run it will be offset by the savings in other diagnostic and consultative approaches. (One of our patients underwent five ophthalmologic consultations, two CT scans, one MRI, optic nerve echography, full-field ERG, various blood studies, and finally cataract extraction before the diagnosis was made).

In summary, the syndrome of acquired foveal cone dysfunction presents as bilateral (but possibly asymmetric), painless, progressive loss of central vision with essentially normal fundi and normal full-field ERG. It may elude diagnosis until focal ERG is performed. Focal ERG abnormalities may precede full-field ERG abnormalities if this syndrome is a forme fruste of a more generalized cone dystrophy. Cases of isolated foveal cone dysfunction need to be followed prospectively to determine if such changes evolve. Our cases expand the clinical spectrum to include ring scotomas that suggest the involvement of adjacent central rods despite a normal full-field rod ERG. Additionally, the finding of subclinical ERG changes in an asymptomatic family member should prompt further study in this area. Although the exact pathophysiology of this entity remains to be clearly elucidated, we encourage other clinicians to be cognizant of its existence and report on their findings.

Acknowledgment: Dr. ten Hove was supported by the McLaughlin Foundation of Canada and is currently affiliated with Queen’s University at Kingston Ontario, Canada. This work was supported in part by an unrestricted grant from Research to Prevent Blindness.

REFERENCES
Occult Maculopathy and the Focal ERG

In this issue of JNO, ten Hove and associates report on three patients with acquired cone dysfunction, whose diagnoses were “secured” by abnormalities in the focal electroretinogram (ERG). In each case, bilateral visual acuity loss, cecocentral scotomas, and color vision disturbance were noted. In case 1, mild temporal optic disc “pallor” was noted while the maculae were considered “normal”. In cases 2 and 3, blunting of the foveal reflex was noted. In these cases, and in others reported, distinguishing optic neuropathy caused by toxic (e.g., alcohol, digoxin, etc.), metabolic (e.g., vitamin B12, folate deficiency) or genetic (e.g., dominant optic atrophy, often occurring in young people) processes from maculopathy on a clinical basis is not always straightforward. When should the clinician consider maculopathy? Always. The question is whether or not the focal ERG is necessary for this purpose.

The symptom of daylight vision impairment (hemeralopia) is certainly not typical of optic neuropathy, and suggests cone dysfunction. The finding of absolutely “normal” maculae on ophthalmoscopy should raise the possibility of an early cone dysfunction syndrome; according to some investigators this is the most frequent funduscopic finding (1). One should recall that “normal” maculae in the face of central visual loss may also be seen in early stages of Stargardt’s disease (and care should be taken to avoid making the erroneous diagnosis of cases of macular branch retinal artery occlusion). I have examined an elderly patient with bilateral visual losses, central scotomas, and color vision defects with “normal” maculae (with contact lens examination) who showed shallow retinal pigment epithelial detachments due to occult choroidal neovascularization on fluorescein angiography. This demonstrates that a “normal” macula on ophthalmoscopy does not rule out maculopathy.

According to Krill and associates (2), fundus findings when noted with cone degeneration include the bull’s-eye lesion (similar to that detected with chloroquine toxicity), diffuse pigment clumping, and regional choroidal vascular atrophy. Fluorescein angiography in such cases may demonstrate subtle changes when ophthalmoscopy is unremarkable. Visual field defects early in the course of the disease may show minor paracentral scotomas (best seen on central 10 degree threshold perimetry), sometimes in a ring distribution, and may spare fixation. Thus, a patient may present with reading difficulty at a time when visual acuity is excellent. Interestingly, optic nerve pallor/atrophy (as in case 1) are not unusual in cone degeneration. Optic atrophy may occur secondary to transsynaptic degeneration (previously called “consecutive optic atrophy”). Heckenlively has reported the finding of temporal optic atrophy along with telangectatic disc vessels (a la Leber’s optic neuropathy) in such patients (3).

Although Krill and associates (2) noted color vision to be normal early in the clinical course of cone dystrophies, by the time the visual acuity was impaired to a 20/40-20/60 level, color vision was usually severely impaired, as opposed to maculopathy in general in which color vision loss more often than not parallels visual acuity loss. Thus, cone degeneration is expected to result in color vision loss out of proportion to visual acuity.

One of the very bothersome findings in all three of Ten Hove’s patients is the “good” color vision relative to visual acuity. In case 1, 6 of 10 Ishihara color plates were correctly identified with each eye at a time when visual acuities were 20/120 and 20/80, respectively. In case 2, “Farnsworth color testing suggested a deuteranopic axis of confusion” when visual acuities were 20/100 and 20/140. I would have expected color vision to have been so poor that determining an axis of confusion would be irrelevant. In case 3, hue discrimination, as tested by Farnsworth D-15 test, was normal in both eyes, although visual acuities were good (20/30, 20/40).

Maculopathy vs. cone dystrophy—how does the electroretinogram help? With diffuse cone dysfunction, the full field ERG will typically demonstrate the following: diminished response to flicker stimuli; abnormal double humped B-wave with the absence of the cone portion after scotopic red stimulus; diminished response to a white light under photopic conditions. The diminished response to flicker stimuli is most specific while the other responses are helpful in cases in which the flicker stimuli result in unreadable artifacts. In cases with normal full field cone response, an abnormal focal ERG (performed with flicker stimuli focused on the macula region only), would imply that the central cones (which represent a minority of the total amount of cones) are abnormal. In fact, impairment of the central cones and/or their connections in the inner retina i.e., Mueller cells which are responsible for the B-wave, will give rise to an abnormal focal ERG.
A caveat: as with any laboratory test, incorrect administration may give rise to false positive results. If the flicker stimulus is misdirected and instead stimulates parafoveal, rather than foveal, cones, a diminished amplitude will be noted (4). Cone degeneration with a preference to macular cones, macular degeneration, Stargardt’s disease, macular scars, and macular branch retinal artery occlusion may give rise to the picture of a normal full field ERG but an abnormal focal ERG. In Ten Hove’s case 3, bilateral cecocentral scotomas associated with ring scotomas were noted. Cone and rod dysfunction were undoubtedly present. With enough photoreceptor abnormalities to result in such a marked diffuse visual field disturbance, why was the full field ERG normal?

Patients with amblyopia, and primary optic atrophy have been shown to have a normal ERG (4). Some years ago, it seemed evident to me that full field ERG would be helpful to “easily” distinguish incomplete central retinal artery occlusion from primary ischemic optic neuropathy. Central retinal artery occlusion eyes should show diminished B-waves compared to their fellow eyes, while anterior ischemic optic neuropathy should, theoretically, be normal. On reviewing the literature at that time, I was dismayed to discover optic atrophy prominently displayed in a list of causes of diminished B-waves (5). The optic atrophy was thought to have to be long-standing, resulting, most likely, in ganglion and bipolar cell (that is, mid-retinal) dropout (transsynaptic degeneration). If some patients with long-standing optic atrophy through retrograde degeneration show abnormalities on the full field ERG, why wouldn’t some patients with long-standing cecocentral scotomas due to optic neuropathy result in diminished focal ERG? The answer is two-fold: 1) Over 60 patients with primary optic atrophy have now been reported as having normal focal ERG (4, 6, 7); and 2) There is no evidence to support the original contention that primary optic atrophy actually results in transsynaptic degeneration or an abnormal ERG (personal communication: Ronald E. Carr, M.D. August 1996).

Laboratory tests alone will not replace clinical acumen, but the focal ERG may be a powerful tool when dealing with visual loss due to occult maculopathies.

Michael L. Slavin, M.D.
Long Island Jewish Medical Center
Great Neck, New York

REFERENCES

The Treatment of Periocular and Facial Pain with Topical Capsaicin

Norah S. Lincoff, M.D., Pamela P. Rath, M.D., and Michio Hirano, M.D.

This article describes the effects of topically applied capsaicin (a nociceptive substance-P suppressor) in patients with neuropathic periocular or facial pain. Peripheral neuropathic pain is a major cause of periocular or facial discomfort and usually follows injury to a subcutaneous peripheral nerve. Though the damage is local, the pain tends to radiate. We studied three patients who complained of a 2- to 30-year history of fluctuating pain in the periocular area. All three had an area of point tenderness that responded to the topical application of capsaicin cream.

Key Words: Periorbital pain—Facial pain—Capsaicin—Trigeminal neuralgia.

Facial pain and, more specifically, periocular pain may be caused by intraocular inflammatory syndromes, migraine, trigeminal neuralgia, or temporomandibular joint pain. Peripheral neuropathic pain is a local phenomenon that can masquerade as a more diffuse headache syndrome, but is actually secondary to direct damage of a subcutaneous peripheral nerve branch of the trigeminal system (1,2). It is usually caused by blunt trauma, postsurgical trauma, or inflammatory disease states.

The treatment of this type of local pain syndrome is challenging because nonsteroidal anti-inflammatory agents (NSAIDs) provide only minimal relief, and narcotics—while effective in moderating pain—can be addictive. Topical capsaicin, which is not an anesthetic agent, acts directly on the damaged nerve ending, thereby interrupting the impulse that causes the central nervous system to perceive pain. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), a component of the red chili pepper, depresses the function of type-C nociceptive fibers by depleting substance P, the principal neurotransmitter of pain, from synaptic terminals (3-6).

Capsaicin has been effective in managing other painful conditions, such as rheumatoid arthritis, diabetic peripheral neuropathy, trigeminal neuralgia, postherpetic neuralgia, and postmastectomy pain (7-17).

PATIENTS AND METHODS

We treated three patients (one man and two women) who suffered from severe periocular pain that we believe was neurogenic in origin (Table 1). All three patients could localize one specific area of tenderness from where their pain syndrome appeared to radiate. The patients had been referred because of failed treatment with at least one of the following medications: NSAIDs, corticosteroids, neuroleptic agents, and antidepressants. Duration of symptoms ranged from 2 to 30 years and was unremitting. The patients described either a deep aching or burning pain (18), but otherwise had normal facial sensation.

The patients were instructed to apply 15 mg of capsaicin cream (0.075%) twice per day to the area of most intense pain. They were told how to apply the cream and were warned to avoid accidental ocular contact. Reassurance was given that the initial burning sensation of the skin would be temporary. The three cases were followed for at least 1 year.

CASE REPORTS

Case 1

This 71-year-old white man was seen in neuroophthalmologic consultation because of a 1-year history of chronic lancinating pain around his left eye; this pain radiated toward the left frontal area. An area over the left infraorbital nerve was the region of the most intense pain and was tender to touch (Fig. 1). Though the patient had no history of trauma, he had undergone cataract surgery with a retrobulbar block to the left eye just prior to the onset of his pain syndrome. Prior to our examination, amitriptyline, nortriptyline, trazodone, and Ativan (lorazepam) were tried with little or no relief. The results of sinus radiographs, computed tomography, magnetic resonance imaging (MRI), complete blood count, determination of the erythrocyte sedimentation rate, and a workup for vasculitis were normal.

Our first examination was on October 27, 1993. His...
The pain was exacerbated by extensive reading. She had definite tenderness on palpation of her right trochlear area. Her pupils were normal. Slit-lamp examination revealed early posterior subcapsular cataracts bilaterally. The findings on exophthalmometry were normal and symmetrical. On external examination, there was obvious point tenderness over the area of specific point tenderness over her right trochlea.

We treated the patient's area of point tenderness with topical capsaicin cream twice a day. He reported dramatic relief of his symptoms by day 10 of treatment. Tapering of the cream to once a day provided continued relief of the patient's neuropathic pain. Discontinuation of the topical treatment at 2 months led to a recurrence of the pain syndrome. Reinstitution of the treatment provided repeat relief of the patient's symptoms within 7 days. The patient continued to have relief of his pain with periodic use of capsaicin cream for 1 year and was then able to discontinue treatment. At 3 years since the initial use of capsaicin, he remains pain free.

Case 2
This 61-year-old white woman presented with a 3-year history of right periorcular pain. Her periorcular pain would at times radiate to the right side of her scalp and down toward her neck, but she could always localize an area of specific point tenderness over her right trochlea. The pain was exacerbated by extensive reading. She never suffered from any symptoms of double vision.

Her past medical history was significant for rheumatoid arthritis and mild hypertension. At the time of her evaluation, she was taking 10 mg of prednisone a day and a NSAlD, with relief of her rheumatoid pain and mild relief of her periorcular pain. Her prior workup, done 1 year before, included an MRI of the brain, the results of which were normal.

Our first examination was on September 7, 1995. Her best corrected visual acuity was 20/25 in each eye. Results of the external examination were significant for mild dermatocchalasis but no periorcular swelling. She had definite tenderness on palpation of her right trochlear area. Her pupils were normal. Slit-lamp examination revealed early posterior subcapsular cataracts bilaterally. Motility was unremarkable, with no evidence of a vertical deviation; superior oblique function was normal bilaterally. Intraocular pressures were normal. Results of a funduscopic examination were unremarkable.

The patient was started on a topical application of capsaicin cream twice a day to the right trochlear area, and her symptoms were relieved within 14 days. She was asked to refrain from extensive reading during the initial treatment period. She was able to taper her dose to once a day, and then to biweekly, with continued relief of her pain at 6 months.

Case 3
This 74-year-old white woman presented with a 30-year history of chronic left facial pain that would radiate from a pinpoint area in the left nasal fold to her left cheek, her periorbit, and occipital area. It was exacerbated by chewing. Intranasally, she could pinpoint the same area of tenderness between her gum and maxillary bone. The pain would become progressively more intense through the day.

In 1983, because of worsening of her symptoms, she underwent an extensive medical workup, which had included an MRI of the brain, computed tomography of the brain, sinus radiographs, orthodontic radiographs, a vascular workup, and temporal artery biopsy, the results of all of which were normal. Past medical treatment trials included Tegretol (carbamazepine), Toradol (ketorolac tromethamine), NSAIDs, and numerous antidepressants with little or no relief. Elavil (amitriptyline) provided some relief at bedtime.

The patient's past medical history was significant for Paget's disease of her left femur and for osteoarthritis. On review of systems, the patient described a significant dental history that included extraction of all of her teeth for cosmetic purposes at the age of 18. She has required chronic dental procedures since that time for proper bridge fittings.

Our first examination was on December 1, 1995. Her best corrected visual acuity was 20/25 in each eye. Slit-lamp examination revealed an early tear-film breakup time but no evidence of keratitis. The pupils were unremarkable, and the intraocular pressures were normal, as were results of the funduscopic examination. She had no facial swelling or redness. Point tenderness was elicited at her left nasolabial fold.

The patient was treated with topical capsaicin cream to her left nasolabial fold twice per day with moderate relief of her local pain and complete relief of her radiating pain.
FIG. 1. Case 1: point tenderness in the area of the left infraorbital nerve and the pattern of the patient's referred pain.

within 14 days. At 9 months, using the cream twice a day, she remains symptomatically much improved.

DISCUSSION

Our cases provide evidence that relief can be obtained for some patients who suffer from periocular pain of neuropathic origin who have failed to improve with standard medical treatment. Capsaicin has been effective in managing other painful conditions, including rheumatoid arthritis, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, migraine, and postmastectomy pain (7-17).

We have treated three patients with capsaicin who suffer from periocular and facial pain felt to be neuropathic in origin. Their pain probably stems from damage or inflammation of terminal branches of the trigeminal sensory system. Patient 2 describes pain in the area supplied by the ophthalmic division of the trigeminal nerve (infraorbital nerve), whereas patients 1 and 3 describe pain along the maxillary division (infraorbital nerve and anterior superior alveolar nerves) (Fig. 2) (18,19). All have obvious trigger points and also suffer from referred pain resembling tic douloureux. This probably occurs because of ephaptic transmission, which is a cause of a more diffuse headache symptomatology (20). Each of the three patients reported a history consistent with prior trauma or inflammation to a branch of the trigeminal nerve. Patient 1 might have incurred damage to his infraorbital nerve during a retrobulbar block. Patient 2 suffers from trochleitis, which is known to be associated with rheumatoid arthritis (21). In trochleitis, the trochlear apparatus, which is a cartilaginous structure, becomes inflamed. This inflammatory process is not always associated with double vision. Patient 3 underwent significant dental work in the past, which might have resulted in local nerve damage. Whether Paget’s disease in this patient is contributory remains unclear.

Our patients were treated twice a day for 1 month and were then allowed to taper their dose as tolerated. Patient 1 was able to discontinue treatment after 1 year without recurrence of pain. Patient 2 improved on a reduced schedule, and patient 3 maintains improvement on capsaicin twice a day. Subjectively, discontinuation of the cream by patients 2 and 3 leads to a noticeable increase in symptoms within 2 weeks.

The effect of capsaicin has been ascribed to its capacity to reduce the level of substance P in sensory fibers (type-C nociceptors). Because this drug is specific for type-C neurons, it affects only sensory pain transmission and not the transmission of touch, pressure, or vibration (3-6). Though capsaicin depletes substance P from synaptic vesicles in the terminal endings of sensory neurons, it does not cause permanent alteration in function; upon discontinuation of the cream, the sensory neurons return to their baseline state (22). This probably explains why all three patients noted at least one recurrence during tapering or following discontinuation of the drug. It is unclear what frequency of application is needed to achieve the optimal therapeutic effect; we chose a twice-a-day schedule of 15 mg to encourage compliance.

Because capsaicin is from the pepper family, ocular exposure causes a transient burning sensation, but does not cause any damage. Patients are instructed to wash their hands with soap and water before and after applying capsaicin. They are asked to use a cotton cloth or cotton ball to wipe clean the area of treatment (wiping in a direction away from their eyes) prior to washing of the face.

The only side effect noted by the three patients was a burning sensation at the site of application, which decreased with continued application of the cream. All three patients noted cessation of the burning within 10
days of the initiation of treatment. No systemic side effects or drug interactions are known to be associated with capsaicin cream (23,24).

These cases indicate that facial and periocular neuropathic pain can be treated with the topical application of capsaicin cream. The patients selected for capsaicin must be able to describe a trigger point. The application of the cream to a larger area of the face for patients who cannot describe a trigger point is not recommended because only a local area of point tenderness seems to be responsive. A prior history of nerve damage from past surgery, trauma, or inflammation is also an important factor in the selection of patients for capsaicin treatment.

REFERENCES

5. Wall PD, Fitzgerald M. Effects of capsaicin applied locally to adult peripheral nerve. I. Physiology of peripheral nerve and spinal cord. Pain 1983;11:363-77.
Follow-up Studies on Pattern Reversal Visually Evoked Cortical Potentials in a 2-Year-Old Child with Optic Neuritis

Kimi Sato, M.D., Emiko Adachi-Usami, M.D., and Atsushi Mizota, M.D.

A 2-year and 7-month-old boy had sudden visual loss in both eyes and showed bilateral optic neuritis without systemic symptoms. Steroid therapy improved his visual acuity from 0.077 and 0.053 to 1.0 at 7 months after onset. Magnetic resonance imaging (MRI) of the brain showed high density in both optic nerves and multiple lesions in the white matter that were enhanced by gadolinium. We considered the diagnosis of demyelinating disease. Follow-up MRI showed no abnormal lesion. Both transient and steady-state pattern visually evoked cortical potentials were nondetectable at the onset, and the P100 component of the transient pattern reversed visually evoked cortical potential appeared to be delayed thereafter. It has since become shorter in parallel with visual acuity improvement.

Key Words: Optic neuritis—Child—Pattern visually evoked cortical potentials.

CASE REPORT

A 2-year and 7-month-old boy was referred to our clinic on April 25, 1995, because of sudden visual disturbance in both eyes. According to his parents, he complained that he could not see, and they noted that he looked blank and did not gaze at anything. He had vomited several times a few days before the parents noticed his decreased vision. The patient’s past medical history and family histories were noncontributory except that he received a measles vaccination on March 17.

On examination, the primary position of his eyes was orthophoric, the diameter of the pupil was 2.5 mm in both eyes, and the pupillary response to light was poor. The optic disks were reddish and edematous with blurred margins in both eyes, and the retinal veins were extremely engorged. The altered vasculature was more pronounced on the right than on the left (Fig. 1A).

The patient was immediately admitted to the hospital and his systemic examination was performed by pediatricians. His general condition was good, and there were no abnormal neurologic signs. Laboratory test results, including a lumbar puncture, were within normal range. The titer of anticaludilipic acid was nil. Studies for viral infection were negative.

Magnetic resonance imaging (MRI) of the brain demonstrated expanded high density at both optic nerves, and abnormal lesions of the white matter of the brain on T\textsubscript{1} were enhanced by gadolinium (Fig. 2A,B). The patient cooperated for the measurement of both transient and steady-state (PVECPs). The responses were nonrecordable with each eye stimulation (Fig. 3).

Visual acuity was 0.077 in the right eye and 0.053 in the left eye by Teller acuity cards (TACs). Because a demyelinating disease or an infectious disease was suspected, he was treated with intravenous prednisolone (2 mg/kg) for 11 days. The high-density abnormal lesions seen on the MRI resolved at 7 weeks (Fig. 4). Thereafter, the prednisolone was reduced. The P100 component of the transient PVECP was still delayed in both eyes. Twenty days after admission, his visual acuity recovered to 0.63 in the right eye and 0.32 in the left eye by TAC. The optic disk appeared to be normal in both eyes. Color vision test with the Okuma plates for children showed normal findings. Binocular vision test was normal. The P100 component of the transient PVECP had become shorter as the visual acuity improved. However, the steady-state response has remained nonrecordable and nonreproducible.

Throughout the admission, no neurologic sign was observed except optic neuritis. Five months after onset, his transient PVECP was normal in both eyes and his visual
acuity was 1.0 bilaterally. However, the steady-state VECP still remained abnormal.

**DISCUSSION**

To our knowledge, our patient represents the youngest patient with optic neuritis ever reported and one in which PVECPs could be recorded without the help of general anesthetic drugs. It is known that optic neuritis in children occurs bilaterally, and the papillitis appeared to resolve quickly with steroid treatment (3,4). These clinical characteristics were similarly found in the present case. Frequently, affected children had flulike symptoms such as headache and nausea before onset. Although our patient showed no such symptoms, it was thought that he was too young to complain about them. If his parents could have observed his daily behavior more carefully, preceding symptoms may have been found. However, they were generally unexpected.

We suspect that the cause of optic neuritis in our patient could have been ADEM, MS, or possibly vaccination. ADEM was not appropriate because the patient showed no systemic neurologic sign. Our patient did have a measles vaccination 5 weeks before the onset. Rikonen reported 18 children with optic neuritis after infection and vaccination (5). Their ages ranged from 5.2 to 14.5 years. The interval between the onset of optic neuritis and the last vaccination varied from 3 days to 10 years. In the author’s study, 10 of 18 children developed MS. We will have to observe our patient long term to decide the cause conclusively.

The transient PVECP in our patient recovered before
the steady-state PVECPs. If we consider the measuring difficulty between transient and steady-state PVECPs, transient PVECP is hardly performed in children. To isolate the P100 component, reversal frequency needs to be much slower than for a steady-state response, which entails a long recording session for the subject. Our patient was very cooperative and produced good results. It has been known (6) that the P100 component of the PVECP can be delayed significantly in patients with demyelinating diseases. Furthermore, this delay may be much longer than that found in optic neuritis from other etiologies (7). In our patient, there was a 15-ms delay of the P100 between the value measured at the beginning of his visual recovery stage and that obtained at the almost recovered stage. The delay was shorter than the value found in patients with demyelinating diseases.

The shortened P100 latency was clearly followed up and correlated with the subjective visual acuity. This feature was noteworthy because a 2-year and 7-month-old patient could hardly cooperate with PVECP testing. The shortened delay in such a child suggests that the cause of his papillitis was less likely to be a demyelinating disease than a vaccination. Despite the recovery of visual acuity, P100 latency remained obviously delayed in patients with demyelinating diseases (6). However, we must continue to observe the patient because no such case has been available.

**FIG. 3.** Transient pattern VECPs to three reversals per second (A) and steady-state pattern VECPs to 12 reversals per second (B) recorded from a patient with optic neuritis. Check size 16 min, contrast 80%, field size 7 x 11 degrees.
FIG. 4. T₁-weighted images (A) and T₂-weighted Fat Sat images with gadolinium injection (B) demonstrated no enhancement of the bilateral optic nerves, 7 weeks after onset.

REFERENCES

Steroid-Responsive HIV Optic Neuropathy

Ben J. L. Burton, M.R.C.P., Alex P. Leff, M.R.C.P., and Gordon T. Plant, M.D.

A 37-year-old man with bilateral optic neuropathy who recovered on steroid treatment is described. He was subsequently found to be human immunodeficiency virus 1 (HIV-1) positive prior to the onset of his visual symptoms; and no other cause of his optic neuropathy could be found. There is some evidence that HIV itself may be a cause of symptomatic optic neuropathy. A spontaneously relapsing and remitting multiple sclerosis-like syndrome has previously been described in HIV-positive patients, and this may present with optic neuritis. A chronic optic neuritis in HIV-positive patients that is not usually symptomatically important has also been described. We review the literature related to these topics and our patient.

Key Words: HIV—Optic neuropathy—Steroid responsive.

Human immunodeficiency virus 1 (HIV-1) infection may be associated with optic neuropathy because of secondary infections due to syphilis, tuberculosis, cryptococcus, histoplasma, herpes zoster, or cytomegalovirus (1–8). More recently, cases have been described in which optic neuritis has occurred in conjunction with a spontaneously relapsing and remitting multiple sclerosis (MS)-type illness in HIV-1-positive patients (9). There has also been a case of an HIV-positive patient who had a spontaneous remission of optic neuropathy not associated with any other pathogens or evidence of MS (10). We report a remarkable case of bilateral optic neuropathy in an HIV-1-positive man whose severe visual failure recovered fully following treatment with steroids. No cause other than HIV-1 infection could be found for his optic neuropathy.

CASE REPORT

A 37-year-old married student from Zaire who had lived in the United Kingdom for 7 years presented with a 3-week history of a sharp pain in his left eye; the pain was unrelated to eye movements. He developed a rapidly progressive decrease in vision in the same eye over the course of a few days. At 2½ weeks after the onset of symptoms, he developed visual loss in his right eye, again progressing over a few days. His only medication was ibuprofen. On admission, he had visual acuity of 2/60 OD and no perception of light OS. His right eye visual field was full to hand movements, but he was unable to identify colors anywhere in the field. The vitreous and anterior segments of both eyes were quiet. Funduscopy revealed peripapillary nerve fiber-layer swelling and hyperemic discs, and fluorescein angiography showed no frank leakage at the disc and minimal staining only (Fig. 1). He had a left relative afferent pupillary defect. His eye movements were normal, and there was no proptosis. He had no accompanying neurological signs or symptoms and was systemically well.

INVESTIGATIONS

Computerized tomographic imaging of his head showed normal intracranial appearances. Results of magnetic resonance imaging (MRI) of his head and orbits were normal, other than high signal on two slices in the anterior part of the left optic nerve and in at least one slice of the right anterior optic nerve (Fig. 2). The findings on chest radiograph were normal. Cerebrospinal fluid (CSF) examination showed protein of 0.67 g/L, glucose of 2.7 mmol/L, and an elevated white cell count of 23/mm³; 78% of the white cells were lymphocytes, 3% reactive lymphocytes, and 17% macrophages. No organisms or fungi were seen. Oligoclonal bands were present in the CSF, and the serum was also positive but with fewer bands. CSF and serum were tested for herpes zoster virus and Epstein–Barr virus by polymerase chain reaction, but these tests were negative. CSF-cryptococcus antigen was negative. CSF treponema serology was negative [rapid plasma reagin (RPR) and Treponema pallidum hemagglutination assay (TPHA)]. CSF angiotensin-converting enzyme (ACE) was 1.29 IU/L (<1.20 IU/L), which was of uncertain significance. Serum ACE was 39 IU/L (16–59 IU/L). Serum treponema serology was negative (TPHA and RPR). A toxoplasma dye test was negative, and a latex agglutination test showed no evidence of toxoplasma exposure. Blood results showed normal glucose, renal profile, and thyroid function. Gamma-glutamyl transpeptidase was marginally raised at 128 IU/L (8–78 IU/L), and total protein was raised at 89 g/L (63–82 g/L), but the results of other liver function
FIG. 1. Fundus photographs of the right and left eyes show the optic discs and the peripapillary region (top panels). At this stage, the left eye had loss of vision for 17 days and the right eye had loss of vision for 9 days. Both discs are mildly hyperemic, and swelling of the peripapillary nerve fiber layer was considered to be present clinically, more marked in the right eye. The fluorescein angiogram shows mild staining of the optic discs bilaterally, although the significance of this is questionable.

tests were normal. Immunoglobulins showed raised IgG at 21.6 g/L (4.0-18.0 g/L) but normal IgA and IgM. C-reactive protein was 8 mg/L (<5 mg/L), and erythrocyte sedimentation rate was 23 mm/h (1-15 mm/h). Autoantibodies and antineutrophil cytoplasmic antibody were negative. The sickle test was negative, serum vitamin B<sub>12</sub> was 1.261 ng/L (223-1.132 ng/L), and folate was 164 µg/L (186-596 µg/L). A Mantoux test was negative. A full blood count showed hemoglobin of 14.7 g/dL, white cell count of 3.1 x 10<sup>9</sup> (lymphocyte count of 1.2 and neutrophil count of 1.6), and a platelet count of 153 x 10<sup>9</sup>/L. He declined an HIV test during this admission.

On the assumption that this was an acute bilateral optic neuritis of inflammatory origin, possibly granulomatous, the patient was treated with a 3-day course of 1 g methylprednisolone intravenously per day. He then started on prednisolone 60 mg once daily. Six days after the start of this treatment, his visual acuity had improved to 6/24 (6/9 with a pinhole) in the right eye and 3/60 in the left eye.

A month later, his visual acuity was 6/9 OD and 6/6 OS. Ishihara plates were all correct with the right eye, but he made four errors out of 13 with the left eye. His steroids were reduced until 12 weeks, at which point his acuity and color vision had returned to normal in both eyes, with full visual fields. He stopped taking steroids after 16 weeks despite being advised to continue with a dose of 10 mg/day, but his vision remained stable.

When he was readmitted 8 months after his original symptoms started, he had a 2-week history of irrational behavior, confusion, poor memory and, on admission, he had developed a global aphasia. MRI scan showed multiple ring-enhancing lesions consistent with cerebral...
FIG. 2. Magnetic resonance coronal short-tau inversion recovery images through the orbits show increased signal in both optic nerves extending more posteriorly on the left (arrow).

toxoplasmosis. He was treated empirically with sulfadiazine and pyrimethamine. He improved for a day or two before becoming much worse and died 3 weeks after admission. His family refused a postmortem. An HIV-1 test was positive (HIV-2 negative), and stored serum from his original presentation 8 months earlier was also tested and this was also positive.

DISCUSSION

The cause of optic neuropathy in HIV patients is often not discovered, and current opinion seems to be that these patients should be treated for syphilis unless there is clear evidence of another cause (11). At least one such case in the literature has been diagnosed as syphilitic optic neuroretinitis on the basis of a good clinical response to penicillin despite negative syphilis serology (12). Our patient was not treated with penicillin, treponemal serology was negative, and he improved with systemic steroids. However, patients with previously positive syphilis serology can lose reactivity on retesting. This occurs in 7% of asymptomatic HIV-positive patients (a similar percentage as the normal population), but in 38% of symptomatic patients who are HIV positive (13). There have been examples of visual improvement following treatment with steroids in cases of optic nerve syphilis, but this has been in the context of intravenous penicillin treatment prior to the initiation of steroids (14). In HIV-positive, untreated syphilitic patients, inappropriate systemic steroid treatment has caused a clear worsening of the patient's condition (although topical therapy can improve associated uveitis) (2,15). Hence, it is not likely that our patient had syphilis.

Cytomegalovirus cannot have been the cause of our patient's optic neuropathy, given the absence of retinal changes and the complete visual recovery (16). Optic nerve head ischemia from posterior choroidal artery involvement causing visual loss with subsequent partial spontaneous recovery has been described in HIV-positive patients. Fluorescein angiography and the complete recovery of vision rule out this diagnosis in our patient (17).

Another possibility is that our patient actually had a granulomatous, steroid-responsive optic neuropathy, such as is seen in sarcoidosis, which was unrelated to his HIV infection. It is difficult to make this diagnosis without histological confirmation. Sarcoidosis and HIV infection have certainly been reported before in the same patient, but it is unclear whether HIV may actually predispose a patient to sarcoidosis (18).

Our patient subsequently died from what was probably either cerebral toxoplasmosis or a cerebral lymphoma. Toxoplasma has been known to cause papillitis and optic neuritis in acquired immune deficiency syndrome (AIDS) patients (19,20), but complete recovery of vision following steroid treatment would not have occurred if this had been the diagnosis in our patient. Lymphoma is a known cause of optic neuritis, and steroid treatment may result in a complete recovery (21). We cannot completely exclude this as a possible cause of our patient's optic neuropathy, although there were no features to suggest infiltration on funduscopy or MRI and he did not have a relapse following withdrawal of steroid therapy.

Our conclusion is that the optic neuropathy we observed in our patient may have been causally related to his HIV infection. It is known that HIV may cause optic neuropathy from secondary infection or neoplastic disease (2), but we found no evidence of any such cause in our case. We cannot exclude this being a coincidental inflammatory optic neuropathy, but, in view of the previously reported cases in which a direct causal link has been proposed between HIV infection and optic neuropathy (22), we believe that if more such cases are reported there will be increasing evidence of a causal link.

From the literature, there appear to be two ways in which HIV infection alone has been implicated in optic neuropathy. Firstly, there is now increasing evidence that HIV involves the optic nerve in a chronic process that may not be symptomatically important. Visual evoked
potentials have been shown to be reduced in HIV-positive patients (23) compared with age-matched controls, although some opportunistic infections and treatment with zidovudine were not controlled for or excluded in that study. Morphological studies have shown that the number of retrobulbar nerve fibers in patients with AIDS is decreased compared with normal optic nerves (24) even in the absence of opportunistic eye infections, and the authors considered that the pattern and extent of optic nerve axon loss were not compatible with all the damage being secondary to retinal infarcts (cotton-wool spots). A significant decrease in color discrimination has also been demonstrated in HIV-positive patients without retinitis (25), although patients with evidence of HIV-related retinopathy were included in this study. Another study has demonstrated the presence of HIV in the optic nerve (26). Infected macrophages have been suggested as the most likely cause of optic nerve degeneration in these patients (26,27).

Secondly, an acute optic neuropathy has been described as part of an MS-like syndrome in HIV-positive patients. Berger et al. (9) have described a series of these patients. In some of their cases, optic neuropathy with spontaneous improvement did occur, and they point out that the chance association of MS and HIV is probably inadequate to explain the number of similar cases they have seen in their institution. A more severe fulminating MS-like leukoencephalopathy has also been described in HIV-positive men (28). It is unclear whether HIV-1 is directly responsible for an illness resembling MS or whether it unmasks a predisposition to develop MS or interacts with other viruses to cause demyelination (29).

Bilateral optic neuropathy with subsequent remission has been reported by Newman and Lessell (22), who described two patients who were HIV positive, one of whom improved with azidothymidine (AZT) and the other improved with oral steroid treatment. Both patients had received prior treatment with penicillin despite negative syphillis serology. Their steroid-treated patient also had a myelopathy consistent with MS. Neither patient had evidence of any infective or malignant cause of the optic neuritis other than HIV. A case of unilateral optic neuropathy that resolved spontaneously has been described in an HIV-positive patient who went on to develop what was thought to be a cerebral lymphoma and subsequently died (10). Once again, there was no evidence of any other infective cause of the optic neuropathy. More recently, HIV-positive patients with severe clinical symptoms of optic neuropathy of unknown cause have shown some recovery with pentoxifylline, although formal studies and case reports have not yet been published (30).

Steroid responsiveness may be a feature of HIV-associated optic neuritis as exemplified by our case and one of the two cases reported by Newman and Lessell (22). We would therefore recommend treatment with steroids in this situation. However, as pointed out by others (11), concomitant treatment with penicillin may be advisable because syphilitic optic neuritis cannot be excluded even in patients in whom syphillis serology is negative.

REFERENCES

2. Gross JG, Sadun AA, Wing NA, Freeman WR. Severe visual loss related to isolated peripapillary retinal and optic nerve head cyto-
3. Golnik KC, Newman SA, Wispelway B. Cryptococcal optic neur-
4. Lipson BK, Freeman WR, Beetz J, et al. Optic neuropathy associ-
5. Yau TH, Rivers-Velazquez PM, Mark AS, et al. Unilateral optic
6. Lipton D, Catalano RA. Herpes zoster optic neuritis in human immune
deficiency virus infection. Arch Ophthalmol 1990;108:
7. Grossniklaus HE, Fecht KE, Tomsak RL. Cytomegalovirus ret-
8. Halperin LS. Neuroretinitis due to seronegative syphilis associated
11. Gross JG, Sadow AM, Li HK. Cytomegalovirus optic neuritis: character-
12. Halperin LS. Neuroretinitis due to seronegative syphilis associated
15. Faoro MS, Rosenbaum JT. Ocular syphilis in patients with human immuno-
deficiency virus infection. Am J Ophthalmol 1989;106:


Late-Onset Leber's Hereditary Optic Neuropathy

E. Todd Ajax, M.D., and Randy Kardon, M.D., Ph.D.

Progressive, sequential visual loss in the left and then right eye was reported in a 73-year-old male over three months. The presence of a family history of visual loss and the lack of other findings in association with bilateral cecocentral scotomata led to a diagnosis of new onset Leber's hereditary optic neuropathy, confirmed by the presence of a mutation at the 11778 position. This case illustrates that Leber's hereditary optic neuropathy may manifest late in life.

Leber's hereditary optic neuropathy is a well-recognized genetic disorder with several point mutations on the mitochondrial genome known to be associated with this condition (1-5). The significance of some of these mutations is uncertain, but three of these mutations at positions 11778, 14484, and 3960 are pathogenic. These mutations lead to amino acid substitutions in highly conserved regions of mitochondrial protein complexes. The most common mutations result in reduced complex-I activity. These mutations may not cause visual symptoms until a threshold is reached through a continued decline in energy production or an exposure to a toxic or metabolic stress within the optic nerve. Approximately 80% of the time, the disease affects men in their 20s. Uncommonly, however, men and women may be affected past the fifth decade.

We recently diagnosed Leber's optic neuropathy in a 73-year-old gentleman with a 3-month history of gradually declining vision. Initially, this began in his left eye, but his right eye was affected within a month. He noticed it when reading and looking at faces, and described it as looking through a "hazy fog." He had difficulty distinguishing colors and contrasts in fabrics. He felt that the visual loss was progressing rapidly and that his vision was declining "nearly daily." His visual acuity 2 weeks after the onset of his difficulties was 20/40 OD and 20/200 OS. Approximately a month later, his visual acuity was 20/100 OD and count-fingers vision OS. When he was evaluated by our neuro-ophthalmology service months after the onset of symptoms, he was able to count fingers at 6 feet OU and had central red desaturation in both eyes. Funduscopic examination demonstrated temporal pallor of the optic discs (Fig. 1) with a cup-to-disc ratio of 0.2. There was no relative afferent pupillary defect. Bilateral cecocentral scotomata were noted on kinetic visual field testing (Fig. 2), and a magnetic resonance image of the orbits and a fluorescein angiogram were unremarkable. He had smoked a pipe for 40 years, but denied cigarette smoking or alcohol use. There was no history of other toxic exposures or metabolic stresses. His vitamin B12, folate, and Venereal Disease Research Laboratory test levels were normal. He reported that a

Manuscript accepted 7/2/97.
From the Departments of Neurology (E.T.J.) and Ophthalmology, Division of Neuro-Ophthalmology (R.K.), University of Iowa Hospitals and Clinics, Iowa City, Iowa, U.S.A.
Address correspondence and reprint requests to Dr. R. Kardon, Department of Ophthalmology (Pomerantz Family Pavilion), University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, U.S.A.

FIG. 1. Fundus photograph of the right optic nerve (left) and left optic nerve (right) on presentation showing only temporal pallor.
great-grandfather had "eye problems." His sister went blind at the age of 36, although an evaluation reported that her "peripheral vision" was intact. The visual loss was attributed to arachnoiditis, and lysis of adhesions was performed that reportedly aborted further progression. Her son also developed central visual loss at the age of 27, which was attributed to heavy alcohol use and was treated with vitamin B₁₂ and multivitamins. His visual loss continued to progress, and he is now legally blind. Because of his family history and the lack of a clear cause for his visual loss, a screen for Leber's hereditary optic neuropathy was performed and revealed the presence of the 11778 mutation. We were unable to determine any coexisting metabolic or nutritional factors that may have predisposed this patient to develop optic neuropathy at this late age. However, he appears to be the oldest individual reported to have developed progressive visual failure from this mutation. Our review of the literature indicates the oldest reported patient to date was 72, with a majority of cases presenting in their 20s. This and other atypical late-onset cases are associated with a poorer prognosis for visual recovery.

Our case illustrates the importance of keeping this diagnosis in mind even in the elderly population, especially in the setting of a suggestive family history and the lack of more common etiologies of optic neuropathy.

Acknowledgment: R.K. is a recipient of the Research to Prevent Blindness Lew R. Wasserman Merit Award. This study was also supported by an unrestricted grant from Research to Prevent Blindness, New York, NY.

REFERENCES

Presumed Bilateral Occipital Neurosarcoidosis

A Case Report

Syndee J. Givre, M.D., Ph.D., and Joel S. Mindel, M.D., Ph.D.

A 37-year-old man with a history of sarcoidosis, hypertension, asthma, depression and prior intravenous drug use presented with complaints of difficulty in finding his way around the house, headache, and blurred vision in both eyes. The symptoms had been increasing in severity over the prior several months. Physical examination showed normal visual acuity, pupil reactions, and fundi but severe, circumferential constriction of the visual fields bilaterally. The visual fields enlarged appropriately on increasing the distance from the patient to the tangent screen. Neuroimaging revealed bilateral, occipital meningeal involvement and parenchymal lesions consistent with sarcoidosis. Treatment with oral corticosteroids produced a mild subjective improvement in the patient's symptoms and stabilized the visual fields, without improving them. This case represents an unusual presentation of presumed neurosarcoidosis involving the visual pathways at the level of the occipital lobes.

Key Words: Neurosarcoidosis—Occipital cortex—Macular sparing—Visual fields—Magnetic resonance imaging.

CASE REPORT

A 37-year-old man with a history of sarcoidosis, asthma, hypertension, prior intravenous drug use, and depression presented to the emergency department with complaints of two episodes of syncope in the 48 h before admission. He also complained of 2–3 months of headache, dizziness, blurred vision bilaterally, right-sided facial numbness, and forgetfulness. The patient specifically noted a feeling of spatial "disorientation" and gave an example getting lost in the hallway of his home despite intellectually knowing where he was. All of the symptoms had progressively increased in severity and frequency over the 6 weeks before admission. The patient denied any fevers, photophobia, or stiff neck. He was admitted for further workup and treatment.

Three years before admission, the patient had presented to another institution with complaints of shortness of breath and headache. A transbronchial biopsy sample obtained via bronchoscopy was consistent with sarcoidosis. Before the present admission, he was maintained on 7 mg of prednisone daily. His other medications included enalapril, methadone, ranitidine, and trazodone.

The patient was a well-developed, well-nourished man with a flat affect. Vital signs and results of the general physical examination were normal. Neurologic examination was significant for decreased sensation on the right side of the face and slow ambulation with normal gait. Ophthalmologic examination was significant for normal visual acuities, normal pupil reactions (including light-near comparison), normal-appearing fundi, and optic nerve heads. Visual fields to confrontation were severely constricted bilaterally. Automated perimetry confirmed this impression (Fig. 1). On tangent screen testing, the area of visual field increased appropriately when the distance from the patient to the screen was increased.

Complete blood count, erythrocyte sedimentation rate, blood chemistries, and thyroid function tests were within normal limits. Testing for human immunodeficiency virus was negative. The blood angiotensin-converting enzyme level was within normal limits on two occasions. A lumbar puncture was performed. The cerebrospinal fluid (CSF) levels of glucose and protein were 64 mg/dl and 29 mg/dl, respectively. The red blood cell and white blood cell counts in the CSF were 15/mm$^3$ and 14/mm$^3$, respectively. CSF cytology showed small, monomorphic lymphoid cells consistent with a reactive inflammatory process. CSF tests for syphilis VDRL and cryptococcal antigen were negative. Immunoelectrophoresis of the CSF was normal. CSF cultures and stains for bacteria, acid-fast bacteria, yeast, and fungi were negative.

A radiograph of the chest was normal. Brain computed tomography (CT) without contrast showed areas of hyperdensity along the falx and tentorium and bilateral, occipital, and parenchymal hyperdensities. These areas enhanced after the administration of intravenous contrast (Fig. 2). In addition, a focal area of hypodensity that did not enhance with contrast was also noted in the right occipital cortex. This area was thought to represent a focal region of infarction or edema. T1-weighted brain magnetic resonance imaging (MRI) performed after the
BILATERAL OCCIPITAL NEUROSARCOIDOSIS

FIG. 1. Automated visual fields performed on the Humphrey HFA II 1-0-A5 field analyzer. The Central 24-2 full-threshold test was used, with a white, size V stimulus. Graytone plots of three sets of visual fields obtained from the left (left) and right eyes (right) are shown. The uppermost set was obtained on the second day of admission, 1 day after the initiation of high-dose corticosteroids. The middle set was obtained 13 days after the initiation of high-dose corticosteroids. The lowermost set was obtained 42 days after the onset of high-dose corticosteroids.

The patient was treated with 60 mg of prednisone daily. He subsequently noted an improvement in his symptoms and was discharged. During the next 14 months, his visual fields remained stable on a slowly tapered dose of prednisone.

DISCUSSION

Sarcoidosis is a systemic, inflammatory disorder. Because the etiology remains unknown, diagnosis is based on a constellation of radiologic, pathologic, and clinical data. Classical chest radiographic findings include bilateral hilar and mediastinal adenopathy. The pathologic hallmark of sarcoidosis is the noncaseating or non-necrotizing granuloma. The most common clinical presentation of sarcoidosis is an incidental finding on chest film (1).

The frequency of clinically evident, neurologic involvement in sarcoidosis is estimated to be 5% (2–6). Neurosarcoidosis also has been demonstrated in the absence of clinical neurologic manifestations (7). In a large study of 694 patients with sarcoidosis, 5.1% were found to have neurosarcoidosis, and of these, 48% initially presented with neurologic complaints (3). Ninety-seven percent of the patients with neurosarcoidosis in this study had other systemic manifestations of the disorder. All portions of the nervous system, both peripheral and central, may be affected by sarcoidosis. Cranial neuropathy is the most common neurologic deficit, with the facial nerve being most frequently involved (2,3,5). Other central nervous system (CNS) manifestations include meningeal infiltration, parenchymal infiltration or mass, hydrocephalus, vasculopathy, diffuse encephalopathy, and seizures.

Our patient had a prior diagnosis of sarcoidosis. His complaints on the present admission were of spatial disorientation and “blurred” vision. However, on neuroophthalmologic examination, he was found to have normal visual acuities, normal pupil reactions and normal appearance of the optic nerve heads but extremely constricted visual fields bilaterally. This combination of administration of gadolinium showed marked posterior fossa dural (including tentorial) enhancement, bilateral occipital gyral enhancement, and bilateral cerebellar folial enhancement. Figure 3A demonstrates the abnormalities seen in occipital cortex on MRI. Both T2 and proton density images showed bilateral occipital parenchymal changes (Fig. 3B and 3C). These abnormalities were interpreted to be consistent with a diagnosis of neurosarcoidosis.

The patient was treated with 60 mg of prednisone daily. He subsequently noted an improvement in his symptoms and was discharged. During the next 14 months, his visual fields remained stable on a slowly tapered dose of prednisone.

FIG. 2. Brain CT obtained after the administration of intravenous contrast. A section at approximately the level of the occipital cortex demonstrating dural and parenchymal enhancement. The right occipital cortex also shows a focal area of hypodensity that does not enhance with contrast. This may represent a localized infarction or edema.

findings is consistent with bilateral occipital (visual) cortical lesions with macular sparing or psychogenic visual loss (8). The first clinical evidence supporting organic CNS disease was that the patient did not exhibit tunnel vision on tangent screen testing.

Although a biopsy specimen was not obtained, neuroimaging supported a diagnosis of CNS sarcoidosis by demonstrating involvement of the meninges around and parenchyma of both occipital lobes. To our knowledge, this patient is unique in having bilateral involvement of the occipital meninges and parenchyma without evidence of any other involvement of the visual system.

FIG. 3. Transverse MRI sections at approximately the level of the occipital cortex. T1-weighted image obtained after the administration of gadolinium demonstrating marked meningeal enhancement, as well as parenchymal involvement (A). T2-weighted (B) and proton density images (C) demonstrating bilateral occipital cortex hypodensities.
BILATERAL OCCIPITAL NEUROSARCOIDOSIS

REFERENCES
A New Clinical Technique for Demonstrating Changes in Eye Acceleration During Horizontal Saccades in Patients with Partial Internuclear Ophthalmoplegias

Peter Brown, M.D.

The eyelid-mounted accelerometer can pick up the acceleration waveform of the eye during horizontal eye movements. The acceleration profile comprises high-amplitude pulsatile activity in the saccade and changes in the level of background ocular microtremor related to eye position. Adducting saccades of 20° were recorded in eight patients with partial internuclear ophthalmoplegias caused by multiple sclerosis and in eight age-matched healthy subjects. The initial pulse of acceleration activity was reduced by 85% in the patients. In the worst-affected cases, adducting saccades were associated only with an increase in the level of background ocular microtremor in the acceleration trace. The results confirm the hypothesis that an internuclear ophthalmoplegia is due to the loss of the pulse signal to ocular motor neurons, with preservation of the step signal in an adducting saccade.

Key Words: Eye acceleration—Internuclear ophthalmoplegia—Ocular microtremor.

Changes in the acceleration recorded during a saccade give an idea of the variation in forces acting on the eye. The fusion frequency of extraocular muscle is ~400 Hz (1), so synchronous fluctuations in the firing frequency of motor units at well below this should be discernible as fluctuations of force and therefore acceleration. Brown and Day (2) recently described two techniques for the recording of eye acceleration. In one, a lightweight accelerometer was mounted to a suction contact lens and, in the other, an identical accelerometer was fixed over the corneal convexity through the closed eyelid. Both techniques gave very similar acceleration profiles during horizontal saccades. In addition, surface-recorded extraocular muscle electromyography mirrored the acceleration activity in both the time and frequency domains, suggesting that the various features in the acceleration waveform were due to the rhythmic and synchronous modulation of eye muscle discharge. Saccades took two general forms: some consisted of 2-3 large pulses of activity, whereas others consisted of an initial big pulse followed by polyphasic activity of higher frequency that continued for the rest of the saccade.

An accelerometer can also be used to record the background microtremor of the eye in the different positions of horizontal gaze (3,4). As with other methods, the predominant frequencies represented in the microtremor are around 40 and 80 Hz (5,6). These frequency peaks may reflect the rhythmic discharge of extraocular eye muscle, because the eye is heavily overdamped and unlikely to exhibit much in the way of resonance phenomena (7,8).

The eyelid accelerometer technique may provide a simple means of recording acceleration profiles during patients' horizontal eye movements. The present investigation was aimed at further validating the technique while demonstrating that this method of recording can be used in patients. With these objectives in mind, patients with partial internuclear ophthalmoplegias (INO's) were studied. The results confirm the hypothesis that an INO is caused by the loss of the pulse in the normal saccadic pulse step signal to ocular motoneurons.

METHODS

Studies were performed with the understanding and written consent of each subject and with approval of the local ethics committee. Eight patients with clinically definite multiple sclerosis were studied (mean age, 43; age range, 24-60 years; four women). Three patients had unilateral and five had bilateral partial INOs. The worst-affected eye was recorded in each case (the mean peak velocity of the adducting eye in horizontal saccades was 167°/s; range, 63-220°/s). Eye movements were also recorded in eight healthy volunteers (mean age, 43; age range, 28-65 years; three women).

Acceleration was recorded by using a linear accelerometer because this was lightweight and yet recorded the pattern of acceleration of the eye (although it did not provide direct recordings of rotational acceleration). The technique has been previously reported in detail (2). The eyelid of one eye was taped gently shut and the acceler-
ometer mounted over the eyelid at the point of maximal convexity (with the cornea and pupil underlying this). Double-sided tape was used to secure the accelerometer to the lid, and the accelerometer lead was taped to the forehead. The accelerometer was orientated so as to be most sensitive to horizontal movements.

The accelerometer consisted of a semiconductor strain gauge bonded to a simple cantilever beam with a mass at its end. The device weighed 0.5 g and had a linear response range (±0.5 dB) up to 500 Hz (EGAXT-50, Entran, Fairfield, New Jersey). The response to acceleration in a plane other than the direction of sensitivity of the accelerometer was <3% of the output to the same acceleration in the device's direction of sensitivity. The accelerometer signal was amplified with a very low-noise, low-distortion instrumentation amplifier (INA 103, Burr-Brown, Tucson, Arizona). Acceleration signals were digitally low-pass filtered 40 dB down at 600 Hz.

Eye movements were recorded by using the monocular electro-oculogram (EOG). Electrodes (9-mm silver discs) were taped just adjacent to the inner and outer canthus of each eye, and a ground electrode was taped to the middle of the subject's forehead. The EOG was amplified (D150, Digitimer Ltd., Welwyn Garden City, Hertfordshire, United Kingdom) with high-frequency and low-frequency responses 3 dB down at 300 Hz and 0.53 Hz, and monitored on an oscilloscope by the experimenter. The level of illumination was kept steady.

Seated subjects were instructed to make self-paced saccades between two light-emitting diodes arranged so as to be straight ahead and 20° in the direction of adduction of the tested eye. They were asked to hold each position of gaze for ~4 s before the next saccade. Head movements were restrained. Each recording session took ~30 min to complete.

All signals were digitized with 12-bit resolution (1401-plus analogue-to-digital converter, Cambridge Electronic Design, Cambridge, United Kingdom), and collected and analyzed on a personal computer by a software package (CED Spike2). The sampling rate was 400 Hz.

**FIG. 1.** Adducting and abducting saccades of the right eye of a patient with a right partial internuclear ophthalmoplegia (INO). A: An extended record showing the monocular electro-oculogram (EOG) and acceleration recorded with an eyelid accelerometer (traces 2 and 3) in the saccades. The traces 4 and 5 are the high-pass-filtered acceleration (40 dB down at 28 Hz) and the rectified and integrated high-pass-filtered acceleration. The slope of the latter trace is proportional to the level of ocular microtremor in each eye position. Record A begins with the eye in the primary position. A pathologically slow adducting saccade is then made (see the differentiated and smoothed EOG in the top trace). The first boxed area has been expanded in B, which shows that pulsatile activity is absent from the acceleration trace during the adducting saccade. The ocular microtremor becomes more pronounced, however, with the eye adducted, as demonstrated by the steeper slope in the bottom trace in A. After a few seconds, the eye returns to the primary position. The second boxed area, which includes the abducting saccade, is shown in greater detail in C. A large acceleration-deceleration pulse is followed by a brief burst of polyphasic activity. The ocular microtremor in A returns to its former level after the saccade.

---

The record begins with the eye in the primary position. A movement. The ocular microtremor becomes more pronounced, however, with the eye adducted, as demonstrated by the steeper slope of the bottom trace (the rectified and integrated high-pass-filtered acceleration) in Fig. 1A. After a few seconds, the eye returns to the primary position. This abducting saccade is shown in greater detail in Fig. 1C. There is a large acceleration-deceleration pulse followed by a brief burst of polyphasic activity. The ocular microtremor in Fig. 1A returns to its former level after this saccade.

Ocular microtremor was also analyzed in the four patients with the lowest peak-to-peak accelerations in adducting saccades. Preliminary studies in four healthy subjects confirmed that the power spectrum of the ocular microtremor recorded with an eyelid-mounted accelerometer is very similar to that recorded with a contact-lens accelerometer (except that the total power recorded with the latter technique is ~2 times greater). Spectra have two main peaks at around 40 and 80 Hz, and the total power in such spectra increases by 31–94% when the eye is adducted or abducted 20° (unpublished observations). Ocular microtremor was analyzed in the patients by first digitally high-pass filtering the acceleration signal so that it was 40 dB down at 28 Hz. This was necessary to remove direct-current offset and activity due to slow head and eye tremor. The high-pass-filtered acceleration signal was then digitally rectified and integrated as in Fig. 1.

RESULTS

The peak-to-peak acceleration recorded in the adducting saccades of the patients was reduced by 85% compared with age-matched healthy subjects (Fig. 2). Similarly, the ratio of the peak-to-peak acceleration in abducting versus adducting saccades in the same eye was very different in patients (mean, 4.8 ± SEM 0.7) and controls (mean, 1.5 ± 0.2; p < 0.001).

Visual inspection of the acceleration traces of adducting saccades in the patient group confirmed that the initial and later pulses of acceleration activity were equally impaired. In the four most severely affected patients, pulsatile activity was absent and adducting saccades were associated only with a step increase in the background ocular tremor in the acceleration trace. This is shown in Fig. 1A for a patient with a partial right INO. The record begins with the eye in the primary position. A pathologically slow adducting saccade is then made (see the differentiated EOG in the top trace). This saccade has been expanded in Fig. 1B, which shows that pulsatile activity is absent from the acceleration trace during the movement. The ocular microtremor becomes more pronounced, however, with the eye adducted, as demonstrated by the steeper slope of the bottom trace (the rectified and integrated high-pass-filtered acceleration) in Fig. 1A. After a few seconds, the eye returns to the primary position. This abducting saccade is shown in greater detail in Fig. 1C. There is a large acceleration-deceleration pulse followed by a brief burst of polyphasic activity. The ocular microtremor in Fig. 1A returns to its former level after this saccade.

We have previously postulated that the vibrations picked up by an accelerometer fixed over the closed eyelid reflect the synchronous discharge of many extraocular motor units (2). Normally, horizontal saccades are thought to be due to a pulse and step change in ocular motor neuron-firing rate in response to signals originating from neurons in the parapontine reticular formation. These signals reach the ocular motor neurons via axons running in the medial longitudinal fasciculus (MLF). The axons of the MLF are thought to be damaged in patients with INOs. Partially damaged axons transmit low-frequency signals better than high-frequency ones (Wedensky phenomenon) and, as a result, the synchronous burst (or bursts) of high-frequency activity comprising the pulse is particularly affected in lesions of the MLF. It is believed that the loss of the pulse leads to impaired acceleration and slow adducting saccades (9,10). Here we confirm that the initial acceleration pulse is indeed diminished in adducting saccades in patients with partial INOs. In the most severely affected cases, the slowed saccade seems to be accomplished solely by the step

DISCUSSION

2,080 Hz. Amplitude and latency were measured by visual inspection using movable cursors on screen. The peak-to-peak acceleration of the initial acceleration-deceleration pulse (defined as the biggest wave peaking within 10 ms of the onset of the saccade as determined by the EOG) was measured for each of 10 successive saccades made in the same direction. The initial acceleration-deceleration pulse was the largest pulse in the saccades of all the controls and patients, with the exception of the adducting saccades in two patients. In these, the maximum amplitude of the later polyphasic acceleration activity was 156% and 205% greater than that of the pulse at the onset of the saccade. The peak-to-peak amplitudes of the initial pulses were averaged to give the peak-to-peak acceleration in adducting and abducting saccades for each subject. Comparisons were made using the Mann-Whitney U test.

Ocular microtremor was also analyzed in the four patients with the lowest peak-to-peak accelerations in adducting saccades. Preliminary studies in four healthy subjects confirmed that the power spectrum of the ocular microtremor recorded with an eyelid-mounted accelerometer is very similar to that recorded with a contact-lens accelerometer (except that the total power recorded with the latter technique is ~2 times greater). Spectra have two main peaks at around 40 and 80 Hz, and the total power in such spectra increases by 31–94% when the eye is adducted or abducted 20° (unpublished observations). Ocular microtremor was analyzed in the patients by first digitally high-pass filtering the acceleration signal so that it was 40 dB down at 28 Hz. This was necessary to remove direct-current offset and activity due to slow head and eye tremor. The high-pass-filtered acceleration signal was then digitally rectified and integrated as in Fig. 1.

Visual inspection of the acceleration traces of adducting saccades in the patient group confirmed that the initial and later pulses of acceleration activity were equally impaired. In the four most severely affected patients, pulsatile activity was absent and adducting saccades were associated only with a step increase in the background ocular tremor in the acceleration trace. This is shown in Fig. 1A for a patient with a partial right INO. The record begins with the eye in the primary position. A pathologically slow adducting saccade is then made (see the differentiated EOG in the top trace). This saccade has been expanded in Fig. 1B, which shows that pulsatile activity is absent from the acceleration trace during the movement. The ocular microtremor becomes more pronounced, however, with the eye adducted, as demonstrated by the steeper slope of the bottom trace (the rectified and integrated high-pass-filtered acceleration) in Fig. 1A. After a few seconds, the eye returns to the primary position. This abducting saccade is shown in greater detail in Fig. 1C. There is a large acceleration-deceleration pulse followed by a brief burst of polyphasic activity. The ocular microtremor in Fig. 1A returns to its former level after this saccade.

DISCUSSION

We have previously postulated that the vibrations picked up by an accelerometer fixed over the closed eyelid reflect the synchronous discharge of many extraocular motor units (2). Normally, horizontal saccades are thought to be due to a pulse and step change in ocular motor neuron-firing rate in response to signals originating from neurons in the parapontine reticular formation. These signals reach the ocular motor neurons via axons running in the medial longitudinal fasciculus (MLF). The axons of the MLF are thought to be damaged in patients with INOs. Partially damaged axons transmit low-frequency signals better than high-frequency ones (Wedensky phenomenon) and, as a result, the synchronous burst (or bursts) of high-frequency activity comprising the pulse is particularly affected in lesions of the MLF. It is believed that the loss of the pulse leads to impaired acceleration and slow adducting saccades (9,10). Here we confirm that the initial acceleration pulse is indeed diminished in adducting saccades in patients with partial INOs. In the most severely affected cases, the slowed saccade seems to be accomplished solely by the step

FIG. 2. Peak-to-peak acceleration recorded with an eyelid-mounted accelerometer in healthy subjects and in patients with partial internuclear ophthalmoplegias (INOs) during 20° adducting saccades made from the primary position. Each value represents the mean of the peak-to-peak amplitude of the initial acceleration-deceleration pulse measured in 10 successive saccades for each subject. The interrupted horizontal lines give the means across subjects. The peak-to-peak acceleration differed in controls (mean, 0.94 ± 0.12 ms-2; p < 0.01) and patients (mean, 0.14 ± 0.04 ms-2).
increase in extraocular muscle activity, manifest as an increase in the microtremor of the eye.

The eyelid-mounted accelerometer technique is easy to use, taking just a few minutes to set up. It is well tolerated by patients and may provide a simple means of recording the detailed acceleration profile of the eye during horizontal eye movements.

Acknowledgment: I thank Dr. P. Rudge and Dr. P. Riordan-Eva for referring some of the patients.

REFERENCES
Ocular Tilt Reaction with Vertical Eye Movement Palsy Caused by Localized Unilateral Midbrain Lesion

Tsutomu Ohashi, M.D., Kikuro Fukushima, M.D., Shinki Chin, M.D., Takayuki Harada, M.D., Kazuhiko Yoshida, M.D., Minoru Akino, M.D., and Hidehiko Matsuda, M.D.

A 60-year-old man developed diplopia and experienced difficulty moving his eyes. Vertical movement of each eye, including vestibulo-ocular reflex and smooth pursuit, was extremely limited. Horizontal eye movements were normal. His head position was tilted toward his left. There was 10 prism diopters of exotropia and 10 prism diopters of right hypertropia. Fundus photographs revealed a clockwise torsion of both eyes. These signs indicate leftward ocular tilt reaction. Magnetic resonance imaging showed a small area of an increased signal intensity localized in the midbrain dorsomedial to the red nucleus on the right side. Based on recent experimental evidence, it may be assumed that the unilateral lesion involving the right interstitial nucleus of Cajal most probably caused leftward ocular tilt reaction in our patient.

Key Words: Ocular tilt reaction—Interstitial nucleus of Cajal—Magnetic resonance imaging.

The ocular tilt reaction (OTR), as defined by Westheimer and Blair (1), is an oculocephalic synkinesis consisting of head tilt, conjugate eye torsion, and hypotropia, all toward the same side (2,3). The direction of OTR is described by the side of the lower ear (2,3).

In contrast to the clear evidence obtained from experimental research on animals regarding meso-diencephalic lateralization of OTR, the evidence from human studies is confusing (2) because the direction of OTR is not in

![Fig. 1](image-url)
accord with lateralization of the lesions (4–6). In addition, the lesions in most of these cases were relatively large, making it difficult to determine the responsible region (5).

We present the case of a patient with OTR and vertical gaze paralysis in which a small causative lesion was located in the unilateral rostral midbrain dorsomedial to the red nucleus as seen by magnetic resonance imaging. The direction of his OTR coincides exactly with the direction predicted from experimental lesion studies of the interstitial nucleus of Cajal (7,8).

CASE REPORT

On November 24, 1995, this 60-year-old man suddenly noticed weakness of his left arm and leg, as well as diplopia, and was admitted to a neurosurgery hospital. On December 11, he was referred to us for evaluation of his eye movement.

Initial examination revealed his best-corrected visual acuity to be 20/60 in both eyes. No abnormalities were found in the fundi. Slit examination revealed a moderate nuclear cataract. His right eye exhibited a slight reduced pupillary response to light. The pupil diameters of both eyes were equal. Horizontal movement of each eye was normal (Fig. 1A), including the vestibulo-ocular reflex and smooth pursuit with a slight abnormality of convergence. Vertical movement of each eye was absent (Fig. 1A), with severe limitation of the vestibulo-ocular reflex and smooth pursuit.

He was unaware that his head tilted 7° toward the left (Fig. 1B) and was unable to correct this tilt voluntarily. In the primary position, his eye position was about 10 prism diopters exotropic and 10 prism diopters of right hypertropic as detected by prism and cover testing. Fundus photographs taken with his head held in an upright position revealed intorsion of the right eye and extorsion of the left eye (Fig. 1C). Neurological examination revealed a slight left hemiparesis, hyperreflexia of the left lower extremity, and positive Babinski sign of the right leg.

T1-weighted magnetic resonance imaging revealed a high signal area suggesting a recent hemorrhage in the midbrain on the right side dorsomedial to the red nucleus (Fig. 2).

DISCUSSION

Our case is interesting in two ways. First, the unilateral midbrain lesion caused both upward and downward gaze paresis. Unilateral midbrain lesions commonly result in only upgaze paresis, because of lesions of the posterior commissure. On the contrary, bilateral midbrain lesions have been reported to exhibit an isolated palsy of the downward gaze. Recently, Ranalli et al. (9) reported that unilateral midbrain lesions caused both upward and downward vertical eye movement disorders. They presented two possible explanations for downward eye movement paresis caused by a unilateral lesion: (a) downward saccade signals decussate in the ventral posterior commissure of Bucher and Burgi and transverse the region of the opposite rostral interstitial medial longitudinal fasciculus (riMLF) before descending to the oculomotor and trochlear motor neurons; or (b) inhibitory burst signals that silence antagonist upward-acting muscles are impaired.

The second interesting point of this case is that, in addition to complete vertical gaze palsy, leftward OTR was caused by a small, localized lesion in the right midbrain.
There are only nine published reports of cases with OTRs caused by meso-diencephalic and medullary lesions. In three of these cases, the lesion was not clearly lateralized (5). In two of these, the direction of OTR was opposite to what was expected based on experimental lesions in cats; that is, it was ipsiversive in the two patients (4,6). The cases of four patients reported by Halmagyi et al. (2) had unilateral meso-diencephalic lesions that produced a tonic contraversive OTR; however, these lesions were large when compared with the lesion in our case.

In animal experiments, the direction of OTR is ipsilateral when electrical stimulation is applied to the rostral tegmentum (1). On the other hand, lesion studies reveal that the direction of OTR is contralateral to the lesion (7,8). In our case with a small unilateral lesion localized in the rostral midbrain, the direction of OTR coincided with the direction of experimental lesion studies applied in the interstitial nucleus of Cajal.

REFERENCES
Saccadic Ping-Pong Gaze

Ken Johkura, M.D., Atsushi Komiyama, M.D., Mari Tobita, M.D., and Osamu Hasegawa, M.D.

Ping-pong gaze (PPG), or short-cycle periodic alternating gaze, consists of horizontal conjugate ocular deviations alternating every few seconds. This alternating gaze has been described as appearing to be smooth. However, our electrooculographic study of four consecutive unconscious patients with PPG showed smooth waveforms in one patient but saccadic cogwheeling in three patients. In one of the three patients with saccadic PPG, a transition from smooth to saccadic waveforms was noted with clinical improvement. Whereas the patient with smooth PPG died immediately, the patients with saccadic PPG survived in a persistent vegetative state. These findings suggest that saccadic PPG is a clinical variant of PPG in patients in a lighter state of consciousness, possibly related to less extensive brain damage.

Key Words: Ping-pong gaze—Short-cycle periodic alternating gaze—Saccadic ping-pong gaze—Electrooculography.

METHODS

Eye Movement Recordings

Eye movements of patients 1–4 were recorded with AC electrooculography (time constant = 16 s). The amplitudes of the eye movements were calibrated using Hirschberg's corneal reflection test (5,10). Spontaneous eye movements, oculocephalic responses elicited by passive head rotation, and cold caloric responses were recorded. The velocities and saccadic waveforms of the eye movements were analyzed only in patient 3 because only his eye movements were recorded with sufficient resolution to permit such analysis.

CASE REPORT

Patient 1

A 20-year-old man was referred to our hospital because of a severe head injury. On arrival he was in a deep coma. Brain computed tomography (CT) showed bilateral cerebral hemisphere contusions with severe swelling. Despite emergency treatment with surgical decompression, the patient remained in a comatose state, with equal and reactive pupils, and flaccid and areflexic extremities. His eyes did not oscillate at that time.

Two weeks after admission, although he remained comatose, the patient developed decorticate posturing. Pupillary and corneal reflexes were normal. He showed symmetrically increased deep tendon reflexes and extensor plantar responses. At this stage, slow, spontaneous, conjugate horizontal eye movements were recognized when the eyelids were raised. A full excursion from left to right gaze took 1.5 s, and then the eyes reversed direction (Fig. 1, Table 1). These movements were saccadic in nature (Fig. 2A). Oculocephalic responses were present in both the horizontal and vertical directions. With cold caloric stimulation, after a latent period of ~10 s, the eyes deviated to the irrigated side and remained there for a few seconds. Then nystagmus with the slow phase directed to the irrigated side appeared and lasted approximately 2 min. A follow-up brain CT demonstrated the bilateral cerebral contusions but no brain stem abnormalities. Auditory brain stem evoked potentials (ABEPs) were normal. Six weeks after admission, the horizontal saccadic alternating gaze disappeared. The patient remained in a persistent vegetative state.

Patient 2

A 65-year-old man was admitted because of a disturbance in consciousness. He had Parkinson's disease treated with levodopa and dopamine agonists for 12
For 2 months before admission, he had convulsions several times a day. Seven hours before admission, he developed status epilepticus. On arrival he showed decerebrate posturing in response to painful stimuli, although he had no convulsions. His pupils were round and reactive. He showed slightly increased deep tendon reflexes and extensor plantar responses. Brain CT disclosed no abnormalities; electroencephalography showed diffuse low-voltage fast activity without epileptiform discharges. Both eyes moved conjugately in a saccadic fashion from one lateral position to the other, each cycle lasting ~3 s (Table 1). This saccadic alternating gaze continued for 5 days. Oculocephalic responses were present in both the horizontal and vertical directions. With cold caloric stimulation, after a latent period of ~10 s, the eyes deviated tonically to the irrigated side for ~1 min, and then the periodic alternating gaze resumed with increasing amplitude until the original oscillation was restored. The patient remained in a persistent vegetative state.

Patient 3

This 67-year-old man suddenly lost consciousness, presumably due to ventricular fibrillation. Cardiopulmonary resuscitation was successful. Four days after admission, neurologic examination showed that he was still in a comatose state with intact brain stem reflexes. A brain CT showed no abnormal findings, and ABEPs were elicited with normal latencies. When the eyes were opened, slow, spontaneous, conjugate horizontal eye movements were noticed. Both eyes moved smoothly and rhythmically from one extreme lateral position to the other, taking ~2 s (Fig. 2B, top; Table 1).

One week after admission, saccadic components were occasionally superimposed upon smooth alternating gaze movements. These saccadic gaze movements consisted of rapid phases that were directed toward the gaze deviation and centripetally directed small slow phases. The velocities of rapid phases ranged from 60 to 100 deg/sec. The frequency of the alternating saccadic deviation was the same as that of the smooth deviation, but the amplitude was smaller than that of the smooth deviation (Fig. 2B, middle). With clinical improvement, the smooth alternating gaze deviation shifted permanently to the saccadic movement (Fig. 2B, bottom). Oculocephalic responses were present in both the horizontal and vertical directions. With cold caloric stimulation, the eyes deviated tonically to the irrigated side for ~90 s, and then the periodic alternating gaze resumed with increasing amplitude until the original oscillation was restored. The patient remained in a persistent vegetative state and responded only to painful stimuli. Two weeks after admission, the horizontal saccadic alternating gaze disappeared.

Patient 4

This 68-year-old man was referred to our hospital because of rapidly progressing disturbed consciousness. Two years earlier, the patient had undergone incomplete surgical removal of a prostatic cancer and was treated by irradiation. One day before admission, he complained of nausea and general fatigue, gradually followed by a decrease in alertness. On arrival, he failed to respond to painful stimuli and manifested hemoptysis, hematuria, and bleeding from gingiva. Laboratory examinations showed severe liver dysfunction with disseminated intravascular coagulation (DIC). A brain CT was unremarkable. Pupils were equal and round and reacted normally to light; corneal reflexes were intact. He showed normal deep tendon reflexes and extensor plantar responses.

When his eyes were opened, both moved smoothly and conjugately from one extreme side to the other, requiring 2 to 2.5 s (Fig. 2C, Table 1). Oculocephalic responses were present both in the horizontal and vertical directions. Smooth periodic alternating gaze continued during head rotation. With cold caloric stimulation, after a latent period of ~10 s, the eyes deviated to the irrigated side and remained there for ~20 s. The patient died 5 h after admission.

DISCUSSION

Fisher in 1967 (1) described an unconscious patient with bilateral cerebral hemisphere infarction whose eyes moved slowly from one horizontal extreme lateral position to the other. Senelick (6) christened such an eye movement abnormality as PPG. Several investigators (2, 3, 8, 11) have reported similar eye movements characterized by short-cycle, spontaneous, alternating conjugate deviation in comatose patients. Although similar eye movements have been reported in a patient with a posterior fossa hemorrhage (6), PPG is considered to be a
sign of bilateral cerebral hemisphere impairment (1-4,8,11) or bilateral disconnection of the cerebrum from the brain stem (12) and is usually seen in unconscious patients. Our four patients showed these neuroophthalmologic features characteristic of PPG.

Periodic alternating gaze deviations also may exhibit a long cycle (13-15); the eyes remain tonically deviated for 1-2 min before shifting to the opposite side. This eye movement is thought to represent periodic alternating nystagmus (PAN) without the rapid phases (5,13-15) and is reported in patients with posterior fossa lesions (13-15). The eye movements seen in our patients are distinct from PAN because of the short alternating cycles.

Clinically, PPG has been described as smooth movements (2,3,6). Recent oculographic studies have demonstrated smooth waveforms with PPG (5,8,9). In contrast, our oculographic study showed saccadic waveforms in patients 1-3. These waveforms had the following features: (a) the amplitude of the eye deviations were smaller than that of smooth PPG; (b) the horizontal eye deviations consisted of rapid phases that were directed toward the eye deviation and centripetally directed small slow phases; and (c) the velocities of rapid phases ranged from 60 to 100 deg/sec. A transition from smooth to saccadic waveforms was associated with clinical improvement in patient 3. Similar cogwheeling was induced by painful stimuli in another reported patient with smooth PPG (5). Caloric testing evoked nystagmus in two of the three patients with saccadic PPG. The patients with saccadic PPG continued to live in a persistent vegetative state, whereas the patient with smooth PPG died immediately after admission. Although the precise mechanisms of smooth and saccadic PPG are unknown, these findings suggest that saccadic PPG is a clinical variant of PPG and that patients with saccadic PPG are in a lighter state of consciousness possibly related to less extensive brain damage than those with smooth PPG.

Acknowledgment: We thank Dr. David S. Zee (Johns Hopkins University, Baltimore, MD) for critically reviewing the manuscript.

REFERENCES


Terminating Attacks of Ocular Neuromyotonia

Avinoam B. Safran, M.D., and Michel Magistris, M.D.

We examined a 30-year-old woman who, for 6 months, had suffered from ocular neuromyotonia, which consisted of episodic ocular depression. Apart from the ocular complaint, her medical history and the clinical findings were unremarkable. The patient discovered that she could terminate each episode of tonic ocular depression instantly by forcefully directing her gaze upward. Stretching the affected muscle might also prove to be an effective way of ending attacks of neuromyotonia in other patients suffering from this condition.

Key Word: Ocular neuromyotonia—strabismus.

Ocular neuromyotonia has been defined as a paroxysmal monocular deviation resulting from spasm of eye muscles (1,2). We report here our observation of a patient suffering from ocular neuromyotonia who found a way of instantly terminating each episode of tonic ocular deviation.

CASE REPORT

This 30-year-old woman complained of intermittent diplopia that had begun insidiously 6 months previously. The episodes lasted for about 30 s to 3 min. Diplopia was mainly vertical. Apart from these complaints, the patient's medical history was unremarkable.

On examination, her visual acuity and visual fields were normal, as were findings on biomicroscopy of the globes and fundi. Her pupils were equal in light and darkness, and reacted well to photic and accommodative stimulation. Her left upper eyelid showed slight ptosis, but no oculomotor synkinesis on gazing down and/or to the right.

During the examination, at intervals of 2–5 min, her left eye showed a slowly progressive depression that increased over ~½ min. Her pupils were unaffected. During these episodes, she reported a pulling sensation in her left orbit. Tonic deviation of the eye was induced by eccentric gaze in any direction, including upward. We observed that she could end the tonic depression of her left eye by forcefully gazing upward for a few seconds. After sustained convergence, relaxation of adduction in the left eye was markedly slowed, a condition that was associated with a slight pulling sensation in the left orbit. Between attacks, motility was normal. Rapid horizontal or vertical saccades, or moderate convergence, did not elicit unusual ocular motor phenomena.

The results of neurological assessment, electro-neuromyographic evaluation, routine blood tests, and cerebral and orbital magnetic resonance imaging were all normal.

Carbamazepine therapy was started at a dose of 200 mg daily progressively increasing to 200 mg three times a day. No improvement was noted, however, and the treatment was stopped after 2 months. The disorder progressively disappeared within a month, but it recurred 1 year later.

DISCUSSION

Our patient showed characteristic signs of ocular neuromyotonia involving muscles innervated by the left third cranial nerve. The condition consisted of episodic apparently tonic contraction of the left inferior rectus muscle, and delayed relaxation of the left rectus internus muscle, following sustained convergence. A third muscle innervated by the left third cranial nerve—the levator palpebrae muscle—showed moderate limitation, a phenomenon already described with this disorder (2).

By 1997, a total of 25 patients with ocular neuromyotonia had been reported in the literature (3): 13 had a history of a tumor at the base of the skull and most had undergone radiation therapy (4). In other observations, the ocular condition was associated with Graves' ophthalmopathy (3) or with carotid artery aneurysm (5). Our patient belonged to the uncommon category of patients suffering from ocular neuromyotonia who do not have a known medical history of such disorders (4).

It is of interest that our patient could terminate attacks of sustained tonic contraction of the inferior rectus muscle by forcefully directing her gaze upward, thereby attempting to elongate the affected muscle. Both in normal subjects and in patients with lesions in peripheral motor nerves, muscular cramps are characteristically enhanced by muscle shortening and released by muscle...
elongation (6–8). This phenomenon may be similar to that observed in our patient when she attempted to end episodes of sustained contraction.

It is uncertain whether all such patients can terminate attacks of neuromyotonia by using this technique. The procedure may, however, prove useful in a number of patients affected by the condition.

REFERENCES
Papilledema in a Man with an "Occult" Dural Arteriovenous Malformation

Timothy J. Martin, M.D., D. Antonio Bell, M.D., John A. Wilson, M.D.

CASE REPORT

A 51-year-old man was evaluated in November 1994 for transient visual obscurations for 2 months. In addition, he reported hearing his "heartbeat" in both ears. He denied headache, vitamin use, recent trauma, or recent weight gain or loss. Visual acuity was 20/15 in each eye, with no relative afferent pupillary defect, normal motility, and normal slit-lamp examination results. Automated perimetry showed mild enlargement of the blind

FIG. 1. Humphrey automated 30-2 perimetry.
spots and scattered threshold loss in the inferior nasal quadrants (Fig. 1A). Bilateral diffuse optic disk edema was present (Fig. 2A). Enhanced magnetic resonance imaging (MRI) of the brain was read as normal. A lumbar puncture showed an opening pressure of 300 mm of water with normal cerebrospinal fluid (CSF). Acetazolamide (500 mg twice a day) was started.

By March 1995 the patient noted increased intensity of the pulsatile tinnitus. The examination was unchanged except that a cranial bruit could now be auscultated over the left retroauricular area. Cerebral angiography confirmed the presence of a suspected dural arteriovenous malformation (DAVM) in the region of the left transverse sinus (Fig. 3). In retrospect, evidence of the DAVM could be identified on the original MRI (Fig. 4). Transarterial particulate embolization was performed and resulted in rapid abatement of the patient's symptoms. Acetazolamide was discontinued.

In May the patient's pulsatile tinnitus returned, although it was less prominent. The visual fields suggested improvement (Fig. 1B), but the papilledema was only minimally improved (Fig. 2B). Opening pressure on lumbar puncture was 410 mm of water.

Angiography was repeated in July, showing recanalization of the DAVM and occlusion of the left sigmoid sinus at the skull base (Fig. 5). Venous pressures in the superior sagittal sinus (SSS) and left transverse sinus were markedly elevated (33 mmHg in the left transverse sinus; 26 mmHg in the SSS). Transarterial embolization of the DAVM with acrylic glue was performed with incomplete closure and only temporary relief of symptoms.

The pulsatile tinnitus recurred in November, and an-
angiography identified persistent feeding arteries. A transvenous approach allowed successful closure of the left transverse and sigmoid sinuses with multiple fibered platinum coils (Fig. 6). Within 2 months there was clear improvement in the patient’s optic disk edema (Fig. 1C), and the patient has remained asymptomatic for over a year.

**DISCUSSION**

The syndrome of idiopathic intracranial hypertension in obese women is a well-described primary entity. However, in men with papilledema, a diligent search for an identifiable cause must be pursued. MRI alone may not be sensitive enough to visualize DAVMs (1). It is unknown whether magnetic resonance angiography and venography (MRA and MRV) would have been diagnostic in this case, because auscultation of an intracranial bruit...
led directly to cerebral angiography. The possibility of a dural sinus abnormality suggests that it is reasonable to include MRA and MRV sequences with the initial MRI evaluation of men with papilledema (and women with atypical presentations). However, angiography remains the standard and must be pursued when clinically indicated, even with normal noninvasive imaging (1–3).

**Acknowledgment:** Photographs and images were prepared by Richard E. Hackel, M.A., C.R.A.

**REFERENCES**

Papilledema in a Man with an “Occult” Dural Arteriovenous Malformation

Timothy J. Martin, M.D., D. Antonio Bell, M.D., John A. Wilson, M.D.

CASE REPORT

A 51-year-old man was evaluated in November 1994 for transient visual obscurations for 2 months. In addition, he reported hearing his “heartbeat” in both ears. He denied headache, vitamin use, recent trauma, or recent weight gain or loss. Visual acuity was 20/15 in each eye, with no relative afferent pupillary defect, normal motility, and normal slit-lamp examination results. Automated perimetry showed mild enlargement of the blind
spots and scattered threshold loss in the inferior nasal quadrants (Fig. 1A). Bilateral diffuse optic disk edema was present (Fig. 2A). Enhanced magnetic resonance imaging (MRI) of the brain was read as normal. A lumbar puncture showed an opening pressure of 300 mm of water with normal cerebrospinal fluid (CSF). Acetazolamide (500 mg twice a day) was started.

By March 1995 the patient noted increased intensity of the pulsatile tinnitus. The examination was unchanged except that a cranial bruit could now be auscultated over the left retroauricular area. Cerebral angiography confirmed the presence of a suspected dural arteriovenous malformation (DAVM) in the region of the left transverse sinus (Fig. 3). In retrospect, evidence of the DAVM could be identified on the original MRI (Fig. 4). Transarterial particulate embolization was performed and resulted in rapid abatement of the patient’s symptoms. Acetazolamide was discontinued.

In May the patient’s pulsatile tinnitus returned, although it was less prominent. The visual fields suggested improvement (Fig. 1B), but the papilledema was only minimally improved (Fig. 2B). Opening pressure on lumbar puncture was 410 mm of water.

Angiography was repeated in July, showing recanalization of the DAVM and occlusion of the left sigmoid sinus at the skull base (Fig. 5). Venous pressures in the superior sagittal sinus (SSS) and left transverse sinus were markedly elevated (33 mmHg in the left transverse sinus; 26 mmHg in the SSS). Transarterial embolization of the DAVM with acrylic glue was performed with incomplete closure and only temporary relief of symptoms.

The pulsatile tinnitus recurred in November, and an-
Angiography identified persistent feeding arteries. A transvenous approach allowed successful closure of the left transverse and sigmoid sinuses with multiple fibered platinum coils (Fig. 6). Within 2 months there was clear improvement in the patient's optic disk edema (Fig. 1C), and the patient has remained asymptomatic for over a year.

**DISCUSSION**

The syndrome of idiopathic intracranial hypertension in obese women is a well-described primary entity. However, in men with papilledema, a diligent search for an identifiable cause must be pursued. MRI alone may not be sensitive enough to visualize DAVMs (1). It is unknown whether magnetic resonance angiography and venography (MRA and MRV) would have been diagnostic in this case, because auscultation of an intracranial bruit...
led directly to cerebral angiography. The possibility of a dural sinus abnormality suggests that it is reasonable to include MRA and MRV sequences with the initial MRI evaluation of men with papilledema (and women with atypical presentations). However, angiography remains the standard and must be pursued when clinically indicated, even with normal noninvasive imaging (1-3).

Acknowledgment: Photographs and images were prepared by Richard E. Hackel, M.A., C.R.A.

REFERENCES
Pseudotumor Cerebri Sine Papilledema with Unilateral Sixth Nerve Palsy

Rohit Krishna, M.D., Gregory S. Kosmorsky, D.O., and Kenneth W. Wright, M.D.,

A 17-year-old woman presented with a history of 1-week of headache and 3 days of horizontal diplopia. Examination revealed 20/20 vision in both eyes, no papilledema, and an abduction deficit in her left eye. Lumbar puncture revealed an opening pressure of 440 mm H₂O. After treatment with acetazolamide, the headache and abduction deficit resolved. Papilledema never developed. This is a unique case of pseudotumor cerebri sine papilledema with a unilateral abduction deficit. We suggest that young women with headache and unilateral abduction deficits may be unrecognized cases of pseudotumor cerebri.

Key Words: Pseudotumor cerebri—Papilledema—Sixth nerve palsy.

Pseudotumor cerebri is characterized by an elevated opening pressure on lumbar puncture examination with normal cerebrospinal fluid (CSF) composition, normal brain scan, and papilledema. Our report is a unique case of pseudotumor cerebri sine papilledema with a unilateral sixth nerve palsy.

CASE REPORT

A 17-year-old woman, weighing 114 kg, presented with 1 week of throbbing holocranial headache radiating from her neck to her forehead and 3 days of horizontal diplopia. The patient complained of nausea, but denied recent viral syndrome, transient visual obscurations, tinnitus, visual aura, trauma, vomiting, numbness, seizures, or use of medication. There was no family history of migraine headaches. Attempts to treat the headache with antibiotics, oral nonsteroidal antiinflammatory agents, and prochlorperazine were unsuccessful.

On examination, visual acuity was 20/20 in both eyes, with normal color vision, no anisocoria or afferent papillary defect, unremarkable anterior segment, normal intraocular pressures, and no papilledema (Figs. 1 and 2). There was an abduction deficit of the left eye (Fig. 3) and full motility of the right eye. Forced duction testing revealed absence of restriction. Evaluation included normal magnetic resonance (MR) imaging, normal MR venogram, and lumbar puncture (which revealed an opening pressure of 440 mm H₂O), glucose 60 mg/dl, protein 11 mg%, and one white blood cell (WBC) per high power field (HPF). The patient had some relief of headache with lumbar puncture. Treatment with acetazolamide 500 mg p.o. b.i.d. was initiated. Ten days later, the headache had decreased, the abduction deficit improved by 50%, and there was no papilledema. At 2-month follow-up, the headache was gone, the abduction deficit had resolved (Fig. 4), and there was no papilledema.

Papilledema is a common, but not necessary, finding for a diagnosis of pseudotumor cerebri. Pseudotumor cerebri with unilateral or asymmetric papilledema has been described in the literature.(1–6) Lipton (7) was first to describe pseudotumor cerebri without papilledema. Marcelis (8) and Mathew (9) reported pseudotumor cerebri without papilledema in patients with chronic daily headache syndrome. Spence (10) reported on nine patients with pseudotumor cerebri without papilledema, seven of whom had a history of closed head trauma. In a case reported by Chari (11), papilledema developed after the diagnosis of pseudotumor cerebri had been secured. The probable cause of asymmetric or unilateral papilledema, or its absence, is best delineated by Hayreh (12) in his landmark work with monkeys. Inflatable balloons placed in different compartments of the brain resulted in increased intracranial pressure, with pressure ultimately conveyed to the optic nerves. Varying communication of the subarachnoid space and optic nerve through the optic canal created variable transmission of the intracranial pressure to the optic nerve head. A block of CSF pressure could occur at the level of the optic canal due to an almost nonexistent subarachnoid space, thereby functionally dividing the intracranial and intraorbital compartments. There have been other purported causes of asymmetric papilledema, such as inflammatory gliosis or congenital anomalies of the optic nerve sheath (13), obliteration of the subarachnoid space by subarachnoid hemorrhage (10), and intermittently increased intracranial pressure allowing axoplasmic flow to equilibrate.
It is possible that our patient did not have increased intracranial pressure long enough or severe enough to produce papilledema, but this suggestion is unlikely because of the duration of her symptoms and the fact that a sixth nerve palsy developed.

Sixth nerve palsies associated with pseudotumor cerebri are commonly bilateral and are believed to be due to intracranial pressure transmitted to the sixth nerves by an undetermined mechanism. Inferior displacement of the pons, with traction on the abducens nerves, is one possible explanation.

The cause of marked asymmetry of abduction deficit in our case is not clear. It is possible that the anatomy of our patient’s sixth nerves differed from one side to the other or that downward brainstem forces were asymmetrically distributed.

In a young woman presenting with a unilateral or bilateral abduction deficit, headache, and no papilledema, a diagnosis of postviral abducens palsy should be entertained. However, abducens palsy is seen more commonly in younger children. It is possible that our patient had an aseptic meningitis, with temporary obstruction of CSF egress mimicking the pseudotumor cerebri syndrome. However, lack of inflammatory cells, and normal protein and glucose levels in the CSF militates against such a possibility. Our patient responded in a typical fashion to acetazolamide, as would be expected with pseudotumor cerebri.

It is possible that other cases of postviral sixth nerve palsies could be cases of unrecognized pseudotumor cerebri without papilledema. We bring this case to attention to provide an alternative explanation for a young woman complaining of headache with unilateral sixth nerve palsy and no papilledema.

REFERENCES


3. Sher NA, Wirtshaffer J, Shapiro SK, See C, Shapiro I. Unilateral
PSEUDOTUMOR CEREBRI SINE PAPILLEDEMA

Bilateral Anterior Ischemic Optic Neuropathy Following Influenza Vaccination

Aki Kawasaki, M.D., Valerie A. Purvin, M.D., and Rosa Tang, M.D., M.P.H.

Optic neuritis is an occasional complication of vaccination. Visual loss can be unilateral or bilateral, and most patients recover substantially without treatment. The presumptive mechanism is an immune-mediated demyelinating injury of the optic nerve. We report two patients who had permanent visual loss following influenza vaccination. Their pattern of visual loss, segmental optic disc changes, and failure of visual recovery were atypical for demyelinating optic neuritis and reminiscent of a primary ischemic injury to the optic nerve. We speculate that an immune complex-mediated vasculopathy following vaccination can cause anterior ischemic optic neuropathy. Clinicians should be aware of this entity because of the less favorable prognosis for visual recovery in these cases.

Key Words: Optic neuritis—Optic neuropathy—Vaccination.

Optic neuritis is an occasional complication of vaccination. Visual loss can be unilateral or bilateral. Optic disc edema may or may not be present acutely. The presumptive mechanism is an immune-mediated demyelinating injury of the optic nerve, and most patients are believed to recover substantially without treatment. We report two patients with bilateral optic disc edema following influenza vaccination whose clinical features suggested an ischemic mechanism of injury.

CASE REPORTS

Case 1

This 47-year-old woman with mild strabismic amblyopia in her right eye (OD) noted decreased vision OD at 1 week after influenza vaccination (October 1994, Indianapolis, IN). This was associated with transient eye pain. Five days later, she developed blurriness in her left eye (OS). She was otherwise healthy and taking no medications.

On examination, her visual acuity was 20/20 in both eyes, but Goldmann perimetry showed a superior arcuate defect OD and an inferior altitudinal defect OS (Fig. 1). There was no relative afferent pupillary defect. Both optic discs were moderately edematous with splinter hemorrhages and cotton-wool spots (Fig. 2).

The results of a complete blood count, metabolic screen, urinalysis, fluorescent treponemal antibody test, vitamin B12, glucose, and folate levels were normal. Serum protein electrophoresis with immunofixation showed a nonspecific polyclonal hypergammaglobulinemia. A Westergren test indicated that the sedimentation rate was mildly elevated at 44 mm/h, but specific vasculitis serologies (antinuclear antibodies, anti-DNA antibodies, rheumatoid factor, complement level, cryoglobulins, antineutrophilic cytoplasmatic antibodies, and anticardiolipin antibodies) revealed no abnormalities.

Cranial magnetic resonance imaging and lumbar puncture with opening pressure and cerebrospinal fluid analysis were normal.

She was treated with intravenous methylprednisolone 250 mg every 6 h for 3 days and then oral prednisone for 14 days. The visual field defects in either eye did not improve and, eventually, segmental disc atrophy appeared. The results of her examination remained unchanged at 1 year (Fig. 3).

Case 2

This 51-year-old woman became febrile with chills and myalgias the day after influenza vaccination (October 1994, Houston, TX). These symptoms resolved over 3 weeks. Four weeks later, she had ear pain, headache, and blurry vision first in her right eye then in her left eye. Examination revealed acuities of 25/50 OD and 20/25 OS with an inferonasal visual field defect OD and a supranasal defect OS. Both optic discs were edematous, worse segmentally superiorly OD and inferiorly OS. Despite intravenous methylprednisolone, her vision progressively worsened over several weeks to count-fingers OD and 20/100 OS.

The results of head and orbit magnetic resonance imaging, lumbar puncture with immunologic cerebrospinal fluid analysis, complete blood count, Westergren sedimentation rate, fluorescent treponemal antibody test, Rochalimaea antibody test, and tests for antinuclear an-
tibodies, antineutrophilic antibodies, anticardiolipin antibodies, and angiotensin-converting enzyme were normal. Fluorescein angiography showed late optic disc staining consistent with disc edema. Her visual function was unchanged at 2 months, and bilateral optic disc atrophy had developed.

COMMENT

The influenza vaccine contains either inactivated whole virus or split viral antigens. The viruses are grown in chick-embryo allantoic fluid and then killed with formalin and purified. Adults receive a trivalent whole virus vaccine, which is a vaccine containing three different viral strains anticipated to be prevalent in the upcoming season/year. It has been speculated that whole, killed virus vaccines such as trivalent influenza or swine influenza vaccination may share similar antigens (molecular mimicry) with CNS proteins. The viral antigens are believed to stimulate an allergic reaction that produces CNS inflammation and demyelination. This immunologic demyelinating response to a vaccine may present clinically as an acute neurologic deficit with good spontaneous recovery.

There are three well-described cases of influenza-vaccine-associated optic neuritis with good visual recovery in the English literature (1–3). Two of the patients...
FIG. 3. Fundus photograph of the right and left optic discs 1 year after onset of visual loss following influenza vaccination. The right optic disc (left) has diffuse atrophy with superimposed inferior segmental pallor, and the left optic disc (right) has significant superior segmental atrophy.

had bilateral disc edema and visual loss. The third patient had a unilateral retrobulbar optic neuritis. All three patients had received steroids in some form, and all eyes recovered fully.

In contrast, influenza vaccine-associated optic neuritis with poor visual recovery has been reported in two cases (4,5). Two possible pathogenic mechanisms can be postulated for the lack of visual recovery. One possibility is that an allergic cross-reaction to viral antigens stimulated optic nerve inflammation and demyelination severe enough to cause direct axonal injury. Another possible mechanism of injury is an immune-mediated vasculitis causing ischemic optic neuropathy. No pathologic examination of vaccination-associated optic neuritis cur-

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patient age/sex</th>
<th>Systemic symptoms</th>
<th>Time to systemic symptoms*</th>
<th>Time to onset of visual loss*</th>
<th>Initial examination</th>
<th>Steroids</th>
<th>Time to recovery*</th>
<th>Final examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicinfang et al</td>
<td>1977</td>
<td>27 M</td>
<td>myalgias, arthralgias, fever</td>
<td>11 days</td>
<td>3 weeks OS</td>
<td>20/15 OD with mild iritis, 20/30 OS with paracentral scotoma and nl fundus</td>
<td>oral prednisone</td>
<td>6 weeks</td>
<td>&quot;nl and equal acuity&quot; OU, no optic atrophy</td>
</tr>
<tr>
<td>Perry et al</td>
<td>1979</td>
<td>58 M</td>
<td>frontal headache</td>
<td>4 days</td>
<td>~1 week OD, 2-3 weeks OS</td>
<td>NLP OD, LP OS, bilateral disc edema</td>
<td>retrobulbar methylprednisolone and oral prednisone</td>
<td>~6 weeks</td>
<td>20/25 OD, enlarged blindspot and interorbital visual field defect OS</td>
</tr>
<tr>
<td>Ray et al</td>
<td>1996</td>
<td>61 F</td>
<td>none</td>
<td>3 weeks OU, then progressive decline</td>
<td>3 weeks OU, then progressive decline</td>
<td>HM OD, LP OS, bilateral disc edema</td>
<td>Intravenous methylprednisolone and oral prednisone</td>
<td>Significant recovery 6 weeks then gradual improvement over 1 year, none by 3 months</td>
<td>20/25 OD, enlarged blindspot, OS</td>
</tr>
<tr>
<td>Cangemi et al</td>
<td>1980</td>
<td>38 M</td>
<td>none</td>
<td>3 weeks OD</td>
<td>CF OD, central scotoma, disc edema</td>
<td>none</td>
<td>none</td>
<td>3 months</td>
<td>CF OD, optic atrophy</td>
</tr>
<tr>
<td>Maccal et al</td>
<td>1982</td>
<td>31 M</td>
<td>none</td>
<td>3 weeks OU</td>
<td>CF OD, central scotoma, disc edema</td>
<td>none</td>
<td>none</td>
<td>2 years</td>
<td>CF OD, optic atrophy OU, same as initial examination, segmental optic atrophy OU</td>
</tr>
<tr>
<td>Kawasaki et al</td>
<td>1997</td>
<td>47 F</td>
<td>eye pain</td>
<td>7 days</td>
<td>7 days</td>
<td>20/20 OD, superonasal defect OD, inferior altitudinal defect OD, then intravenous SoluMedrol then oral prednisone</td>
<td>none</td>
<td>none</td>
<td>CF OD, 20/100 OS, bilateral optic atrophy</td>
</tr>
<tr>
<td>Kawasaki et al</td>
<td>1997</td>
<td>51 F</td>
<td>fever, myalgias, headaches</td>
<td>1 day</td>
<td>4 weeks</td>
<td>20/25 OD, inferior nasal defect OD, then oral prednisone</td>
<td>Intravenous SoluMedrol</td>
<td>none</td>
<td>CF OD, 20/100 OS, bilateral optic atrophy</td>
</tr>
</tbody>
</table>

*All time is given from the day of influenza vaccination.

---

il = normal; M = male; F = female; NLP = no light perception; LP = light perception; ONSF = optic nerve sheath decompression.
rently exists to help differentiate these two mechanisms of injury. The details of all five cases are summarized in Table 1.

Our two patients share similar clinical features. Both patients noted visual loss in one eye with eye pain or headache within 4 weeks of an influenza vaccine in 1994. Involvement of the second eye occurred shortly thereafter. Bilateral optic disc edema and nerve fiber bundle visual field defects were acute findings in both patients. Despite steroid treatment, both failed to have any visual improvement and eventually developed optic atrophy. An immune-mediated demyelinating injury of the optic nerve that was severe enough also to cause secondary axonal injury with subsequent poor recovery would seem an unlikely mechanism in our first patient, who maintained 20/20 acuity at all times but developed only the permanent field defects. In our two patients, we feel that the pattern of visual field loss, segmental disc changes, and failure of visual recovery is more consistent with anterior ischemic optic neuropathy (AION) than with demyelinating optic neuritis. Because of the close temporal relationship to influenza vaccination and the bilateral involvement, we speculate that the mechanism of AION in our two patients may be an immune complex-mediated vasculopathy. This presumptive mechanism might also account for the systemic symptoms experienced by one of the patients (case 2) prior to visual loss and for abnormal serum markers (elevated sedimentation rate and polyclonal hypergammaglobulinemia) in our other patient (case 1).

We remind clinicians to consider influenza vaccination as a potential etiology for patients who present with visual loss and disc edema, especially bilaterally, within several weeks of vaccination. A nerve fiber bundle pattern of visual field loss and/or segmental disc swelling are more characteristic of ischemic rather than demyelinating injury and may be indicators for a less favorable prognosis.

Acknowledgment: This research was supported by the Midwest Eye Foundation at Methodist Hospital and a Research to Prevent Blindness grant.

REFERENCES

Optic Nerve Head Swelling in the Hadju–Cheney Syndrome

Karl C. Golnik, M.D., and Robert C. Kersten, M.D.

The Hadju–Cheney syndrome is one of the idiopathic acro-osteolyses. Associated neurologic abnormalities are often a result of progressive basilar invagination. A 48-year-old man with the Hadju–Cheney syndrome developed progressive bilateral visual loss. On examination, he had hyperopia, choroidal folds, optic nerve head swelling, and mild optic neuropathy. Computed tomographic scans showed massive enlargement of both intraorbital optic nerve sheaths. Improvement occurred after optic nerve sheath fenestration. Visual loss due to optic nerve meningocele can occur in the Hadju–Cheney syndrome. Optic nerve sheath fenestration can result in visual improvement. It is unclear whether the occurrence of optic nerve meningocele is causally or fortuitously related to the Hadju–Cheney syndrome.

Key Words: Hadju–Cheney syndrome—Optic nerve meningocele.

Idiopathic acro-osteolysis is characterized by painful osteolysis of the distal phalanges. The Hadju–Cheney syndrome is one of the idiopathic acro-osteolyses further characterized by dolichocephaly, open cranial sutures, basilar invagination, multiple wormian bones, early loss of teeth, characteristic facies, and short stature (1,2). A variety of neurologic conditions, including cranial nerve palsies (1,3), trigeminal neuralgia (4), hemifacial spasm (5), syringohydromyelia (6), and hydrocephalus (7,8), have been associated with this syndrome. Reported ophthalmologic abnormalities include nystagmus (1), hypertelorism (4,6,8,9), and optic disc pallor (1,9). We report the case of a patient with the Hadju–Cheney syndrome and visual loss due to massive enlargement of both intraorbital optic nerve sheaths.

CASE REPORT

A 48-year-old man complained of gradually decreasing vision over several years. His refraction had become two diopters more hyperopic over the preceding 18 months. In December 1995, he was noted to have right optic nerve head swelling and referred for neuro-ophthalmic examination. At that time, he noted episodes of unilateral and bilateral visual loss of 5–10 s in duration. He denied tinnitus and diplopia. There had been no change in headache frequency or character, which he described as weekly, frontal, and stress related. His past medical history included only loss of all teeth in his mid-20s, and over the past 5 years he had required several reconstructive joint surgeries, including compressive groove plate fixation of the left wrist. At 18 months prior to our evaluation, the Hadju–Cheney syndrome had been diagnosed, based on radiographic appearance, loss of teeth, and external appearance.

Examination revealed that the patient had a broad forehead, hypertelorism, a sunken midface (Fig. 1), and

Manuscript accepted 7/30/97.
From the Department of Ophthalmology (K.C.G.), University of Cincinnati; and Cincinnati Eye Institute (R.C.K.), Cincinnati, Ohio, U.S.A.
Address correspondence and reprint requests to Dr. K. C. Golnik, 10494 Montgomery Road, Cincinnati, OH 45242, U.S.A.
marked clubbing and shortening of his digits (Fig. 2). He was 66 inches tall and weighed 132 pounds. Visual acuity was 20/25 OD, 20/20 OS with correction of +5.00 + 1.50 × 01 OD and +4.50 + 1.25 × 01 OS. He correctly identified 9 of 10 Hardy–Rand–Rittler color plates OD and 10 of 10 OS. His pupils were briskly reactive with an equivocal right relative afferent pupillary defect. Automated static perimetry showed mild enlargement of both blind spots and generalized depression OD > OS (Fig. 3). His ocular motility was normal. Fundoscopy showed mild right optic nerve head swelling and bilateral choroidal folds (Fig. 4).

Neuroimaging was the first diagnostic consideration because of his known underlying condition. Magnetic resonance (MR) images could not be obtained because of numerous orthopedic metallic fixation plates. The results of computed tomography of the brain were normal, but massive enlargement of both intraorbital optic nerve sheaths was apparent; both optic nerves appeared normal (Fig. 5). Basilar invagination was not present, and ventricles were normal in size. Lumbar puncture showed both normal opening pressure (100 mm H₂O) and cerebrospinal fluid (CSF) composition. Right optic nerve sheath fenestration was performed via the lateral approach (10). The nerve sheath was markedly distended and bluish. Serosanguinous fluid escaped as the sheath incision was made. Sheath biopsy showed noninflammatory fibrous tissue consistent with normal arachnoid sheath. Postoperatively, transient visual obscurations ceased and visual field improved (Fig. 6), as did right optic nerve head swelling (Fig. 7).

**DISCUSSION**

Dissolution of bone in the phalanges (acro-osteolysis) can be idiopathic or a result of a variety of insults, in-

---

**FIG. 2.** A: There is marked shortening and thickening (pseudoclubbing) of all digits. B: This radiograph shows loss of calcium in all phalanges (acro-osteolysis).
Acro-osteolysis has been reported in association with scleroderma, sarcoidosis, and rheumatoid syndromes (11-13). The idiopathic acro-osteolyses are generally divided into three groups based on the pattern of bone involvement: (a) phalangeal, (b) tarsocarpal, and (c) multicentric (14). The Hadju-Cheney syndrome (type VI idiopathic osteolysis) is multicentric and characterized by acro-osteolysis, cranial osteodysplasia, and generalized osteoporosis of vertebrae and long bones. Afflicted individuals have characteristic facies (midfacial flattening, receding chin, and low-set ears), premature loss of teeth, occipital prominence, joint laxity, pseudoclubbing of digits, and short stature (1-9). Recently, cystic renal disease has been considered an important component of this syndrome (15). Inheritance is either autosomal dominant or sporadic (1,2,5,16,17).

Neurologic impairment is usually related to basilar invagination, which can result in marked angulation of the brainstem, redundancy of blood vessels, and impairment of CSF outflow. Resulting pressure and/or stretching of cranial nerves has been reported to cause trigeminal neuralgia (4), corneal anesthesia (3,5), ophthalmoplegia (1,3), hemifacial spasm (5), and hearing loss (1,9,14). Ophthalmoplegia may result when one or both abducens nerves are affected by direct compression, stretching, or increased intracranial pressure. Oculomotor and trochlear nerve palsies have not been reported. Hydrocephalus may require neurosurgical intervention (7, 15).

Afferent visual system involvement seems to be limited to the optic nerve. Although hydrocephalus is occasionally reported, only one patient has been observed to have papilledema (8). That patient had visual acuity of 6/6 OD and 6/9 OS, but no other details of the ophthalmologic examination were provided. It is unclear whether other patients with hydrocephalus had ophthalmologic examinations (7,15). Unilateral and bilateral optic atrophy has been reported, but the etiology is unclear (1,9). Kawamura et al. (3) found "symmetric fluid collections around the optic nerves in the orbits" on MR images of a 32-year-old man with Hadju-Cheney syndrome. No hydrocephalus was present, and the appearance of the optic nerve heads was not reported.

Our patient had acro-osteolysis, pseudoclubbing, short stature, generalized osteoporosis, typical facies, and premature loss of teeth, thus fulfilling the diagnostic criteria for the Hadju-Cheney syndrome. He also had progressive hyperopia, right optic nerve head swelling, bilateral choroidal folds, and impressive enlargement of both intracranial optic nerve sheaths. The optic nerves themselves and the CSF signal within the sheath appeared normal.

Enlargement of the optic nerve-sheath complex has been reported in association with a variety of conditions (18,19). High-resolution computed tomographic scan or MR imaging can usually distinguish whether there is optic nerve enlargement, distention of the sheath, or thickening of the sheath. Isolated optic nerve enlargement is most often seen as a result of infiltration (glioma, metastasis, or sarcoidosis) or inflammation (optic neuritis) (18,19). Isolated optic nerve sheath thickening may result from meningioma or periocular neuritis (20). Distension of the subarachnoid space is well recognized as accompanying optic nerve glioma (arachnoidal gliomatosis) in patients with neurofibromatosis type I (21-24). Rarely, cystic enlargement of the nerve sheath has been reported associated with nerve sheath meningioma (25), tumors at the orbital apex (26), and trauma (27).

Dilation of the nerve sheath and expansion of the sub-
HADJU-CHENEY SYNDROME

FIG. 4. Optic nerve heads at presentation. A: The right optic nerve head was mildly swollen. B: The left optic nerve head was normal. Radial chorioretinal folds were present in both posterior poles.

Arachnoid space with normal optic nerve appearance is usually a result of increased intracranial pressure (18,19,28-31). Although our patient had a normal opening pressure, we can not absolutely rule out pseudotumor cerebri, because pressure fluctuations can occur in this condition. However, our patient had no other symptoms or signs of increased intracranial pressure. Additionally, our patient had unilateral disc swelling and, although this can occur with pseudotumor cerebri, it is thought to do so because of poor communication of CSF pressure along the orbital optic nerve. Our patient had bilaterally markedly distended nerve sheaths, and it would seem that if elevated pressure caused the distension, then bilateral disc swelling should be present.

A variety of terms have been used to describe nerve sheath enlargement associated with normal optic nerve appearance in the presence of normal intracranial pressure. These include optic nerve arachnoid cyst (25,32-36), periorbit hygroma (36), optic nerve ascites (37), and meningocele (31). It may occur unilaterally (31,33,38,39) or bilaterally (31,36). An association with optic nerve coloboma has been reported (32,36). Patients often have optic disc swelling (36,39), but atrophic (31,33,38), and initially normal (31,36), nerve head appearance has been reported. Gradually progressive optic neuropathy can result in visual loss (31,33,38,39). Alternatively, choroidal folds and progressive hyperopia may lead to visual complaints (31). Dailey et al. (40) described seven patients who developed progressive hyperopia and choroidal folds; six of seven also had enlarged optic nerve sheaths. Presumably, some degree of pressure is exerted on the nerve and globe. Indeed, visual loss can be arrested (31,36) or reversed (31,39) by fenestrating the optic nerve sheath.

Garrity et al. (31) have used the term meningocele to describe any saccular dilation of the optic nerve sheath. Therapeutically, it is important to differentiate between primary meningoceles: those without other abnormalities of the optic nerve or sheath and secondary meningoceles: those associated with tumor, infiltration, or inflammation. We feel that primary optic nerve meningoceles can be followed if no visual loss is present, but optic

FIG. 5. Computed tomographic scan at presentation. Axial view showing enlargement of both optic nerve sheaths; note the flattening of the posterior aspect of each globe.
nerve sheath fenestration should be considered if optic neuropathy develops. Our patient had primary, bilateral optic nerve meningoceles, and we elected to fenestrate the nerve with dysfunction. Neuroimaging is essential to rule out basilar invagination, hydrocephalus, and meningocele in any patient with the Hadju-Cheney syndrome.

Even asymptomatic patients may have early basilar invagination and/or hydrocephalus.

REFERENCES

27. Hupp SL, Buckley EG, Byrne SP, Tezel RR, Glauser JS, Schatz
HADJU–CHENEY SYNDROME


Literature Abstracts—Europe

H. Esriel Killer, M.D.


A total of 325 patients with dry eyes were divided into those responsive to topical treatment and nonresponders. Fifty-seven percent of the treated unresponsive patients were diagnosed with Meige’s syndrome. This article stresses that patients not responding to conventional treatment of dry eyes should be recognized. Whether that surprisingly high number of patients with Meige’s syndrome can be reproduced in a non-Japanese population must be studied.


Sometimes too many words lower the essence of the object they describe. This major paper on papilledema should not be summarized but studied and enjoyed. So do it!

Ocular Neuromyotonia in a Case of Paget’s Disease of Bone. Boschi A, Spiritus M, Cioffi M, Devogelaer JP, Bergmans J. Neuroophthalmology 1997;18:67-71. [Reprint requests to Dr. Antonella Broschi, Department of Ophthalmology, St. Luc University Hospital, UCL University, 10 Hippocrate Avenue, 1200 Brussels, Belgium.]

Ocular neuromyotonia is a rare disorder that manifests with short episodes of binocular diplopia. This article reports a case of ocular neuromyotonia in a 72-year-old woman with Paget’s disease. The authors present this case with nice electromyographic recordings of the involved medial rectus muscle at rest and during diplopia episodes. The treatment of this bothersome condition consisted of oral carbamazepine.


How to treat multiple sclerosis is still an issue of (regional) preference. The same is true for the management of optic neuritis, although recommendations can be drawn from the optic neuritis treatment trial. Barnes and colleagues studied the outcome of oral and intravenous methylprednisolone therapy in 80 patients with the relapsing form of multiple sclerosis (double-blind placebo-controlled trial). The results were clinically measured using the Kurtzke’s expanded disability status scale and Hauser’s Ambulatory Index and arm-function index. There were no significant differences between the two groups at any stage in the study. The authors recommend that it is therefore preferable to prescribe oral rather than intravenous steroids for acute relapses in multiple sclerosis for “reasons of patient convenience, safety and cost.” Whether the same recommendation might be used for the treatment of optic neuritis needs to be evaluated.

Contrast Sensitivity in Benign Intracranial Hypertension. Stavrou P, Honan WP. Neuroophthalmology 1997;17:127-34. [Reprint requests to Dr. W.P. Honan, Royal Devon and Exeter Hospital, Wonford, Barrack Road, Exeter, EX2 5DW, England.]

The management of benign intracranial hypertension (BIH) depends on the severity of visual loss. As seen in other etiologies for papilledema, the fundus appearance and the loss of visual function (visual acuity, color vision, visual field, etc.) does not have a strict correlation. In order to administer the best treatment, early functional defects should be diagnosed. This article evaluates the practical role of contrast sensitivity testing in patients with BIH. Twenty-six eyes of BIH patients were tested and compared with those of a matched control group. The visual acuity in the BIH group was normal in 22 eyes. However, contrast sensitivity was significantly reduced in the BIH group at all spatial frequencies. Contrast sensitivity therefore is more sensitive than Snellen visual acuity and represents a valuable tool in assessment and follow-up in patients with BIH.

Part I

*Larry P. Frohman, M.D., and *Paul Lama, M.D.

Systemic illnesses, such as vasculitides and systemic lupus erythematosus, may have ocular symptoms, or they may present with ocular signs and undiagnosed or occult systemic signs. The recently described ophthalmic and neurologic presentations and new diagnostic modalities for Wegener’s granulomatosis, giant cell arteritis, and systemic lupus erythematosus are reviewed. Hypercoagulable states and their role in visual diseases are assessed, and strategies for evaluating patients with hypercoagulable states are described.

This article updates the review that appeared in this journal in two parts (1,2). The article reviews recent reports in the literature regarding systemic illnesses that may cause neuro-ophthalmic signs. Whereas the emphasis is specifically on the diagnosis, etiopathogenesis, and therapy of the neurologic or ophthalmic manifestations of these illnesses, articles reporting significant progress in the understanding of the systemic illness have been reviewed. This part of this recurrent series concentrates on the vasculitides that the neuro-ophthalmologist would most likely encounter, namely Wegener’s granulomatosis (WG) and the giant cell vasculitides.

Recent information on systemic lupus erythematosus (SLE) is reviewed, as is the role of antiphospholipid antibodies (APA) in producing neurologic and ophthalmic disease. Finally, other specific causes of thrombosis responsible for neurologic and ophthalmic symptoms are discussed. In a future issue, the next part of this periodic review will cover recent advances in knowledge of infectious and related illnesses (including AIDS) and sarcoidosis.

VASCULITIS

Wegener’s Granulomatosis

Wegener’s granulomatosis is a necrotizing vasculitis with a predilection for the upper and lower respiratory tracts, with glomerulonephritis a common feature. In 1990, the American College of Rheumatology established criteria for the classification of WG. These are as follows: (1) oral or nasal inflammation manifested by oral ulcers or purulent or bloody nasal discharge; (2) abnormal chest roentgenogram with nodules, fixed infiltrated, or cavities; (3) abnormal urine sediment with erythrocyte casts or microhematuria (more than five erythrocytes per high-power field); and (4) granulomatous inflammation within the wall of an artery or arteriole. The nervous system is ultimately involved in 22% of cases, and the visual system in 60% of cases. Ocular signs may be the presenting signs of Wegener’s in up to 17% of cases.

The most common neurologic manifestations are peripheral neuropathy (mononeuritis multiplex) or cranial neuropathy. Cranial nerves II, III, IV, and VI are the most commonly affected. Hearing loss is a common finding from mechanisms such as cochlear nerve involvement or chronic otitis from Eustachian tube blockage. Neurologic foci may occur as a direct extension from the paranasal sinuses or orbit, from cerebral or meningeal granulomatous inflammation, or from central nervous system (CNS) vasculitis.

Episcleritis, scleritis, marginal corneal ulceration, and uveitis are typical ocular signs. Granulomatous involvement of the paranasal sinuses, lacrimal glands, and orbit are frequently seen. Choriocapillaritis, retinal vasculitis, or optic neuropathy may lead to visual loss (3).

New or infrequently seen neurologic and ophthalmic signs of WG have recently been reported. Tullo and coworkers describe four patients, all with active WG, who developed florid xanthelasma as a sign of WG. Lesions were asymmetric, were worse on the side with worse orbital inflammation, and resolved or improved with therapy. The researchers point out that a markedly yellow eyelid, especially in the presence of orbital inflammation, suggests WG (4).
Wegener’s granulomatosis may present in a manner mimicking other neuro-ophthalmic syndromes. Gobel and others report on a 58-year-old woman who presented with a painless breast mass. This led to evaluation of a year of orbital inflammation (previously diagnosed as orbital pseudotumor) and 6 months of trigeminal neuralgia, as well as a pulmonary nodule. The specimens from both the exenteration of the blind eye and the breast mass were consistent with WG (5).

Agostini and associates report on a patient in whom ocular WG mimicked malignant melanoma. This patient was believed to have a choroidal melanoma, and had a history of angina pectoris and no respiratory disease. Scintillography results for malignant melanoma were falsely positive. A positive finding on antineutrophilic cytoplasmic antibody (ANCA) assay led to open-lung biopsy, which led to the diagnosis of WG. The ocular symptoms resolved with treatment using corticosteroids and cyclophosphamide (6).

Other manifestations seen in the head may be presenting signs of WG. Ah-See and colleagues report the first case of WG that presented as isolated and widespread involvement of the major salivary glands (7). WG limited to the salivary gland tends to be more limited and to carry a better prognosis. This patient did well with immunosuppressive therapy.

Facial nerve palsy is seen in the course of WG but rarely is the presenting sign. Typically, such cases have had a protracted diagnostic evaluation until the underlying WG has been established as the etiology of the facial palsy. Hern and others report on a patient in whom the discovery of an elevated erythrocyte sedimentation rate led to obtaining an abnormal ANCA assay result. Nasal mucosal mucosa biopsy established the diagnosis (8).

Neuro-ophthalmic signs may be present before overt systemic disease is present, or before serologic evidence of the underlying process is available. Newman and colleagues report on four patients with the limited form of WG who presented with neuro-ophthalmic findings (9). All four had motility disturbances at presentation: one with oculomotor and trochlear paresis, one with oculomotor paralysis, one with trochlear and abducens paresis, and one with a horizontal gaze deviation. Other neurologic findings in the series included headache, seizures, confusion, focal weakness, dysphagia, and dysphonia. Other cranial neuropathies seen in this group included facial, acoustic, glossopharyngeal, vagus, accessory, and hypoglossal paresis. Magnetic resonance (MR) imaging abnormalities in this series included meningeal enhancement and thickening, gyral enhancement, and T2 white matter abnormalities. The initial ANCA assay results were normal in all four; one developed a positive reaction later. All had necrotizing granulomatous inflammation. Thus, in this series, meningoencephalitis inflammation preceded either systemic symptoms or laboratory abnormalities.

Wegener’s granulomatosis may have hypothalamic dysfunction caused by meningeal and intracerebral inflammation. Czarnecki and Spickler report a case where WG caused an elevated prolactin level and diabetes insipidus. The initial T1-weighted MR imaging scan demonstrated a isointense heterogeneous mass in the sella; contrast revealed a thickened infundibulum, with both the infundibulum and hypothalamus enhancing. The imaging findings nearly resolved with steroid therapy (10).

Foster and others report a case of WG where the initial signs were an optic neuropathy and contralateral ophthalmoplegia with suprathalamic anesthesis. This 26-year-old man had a history of 11 years of nasal crusting, nonpurulent blood-tinged discharge, and occasional episcleritis after a polypectomy and ethmoidectomy. Despite a negative finding on ANCA assay, deep nasal biopsies revealed small vessel vasculitis with necrosis consistent with WG, and therapy with cyclophosphamide and prednisone led to recovery of vision and ocular rotations (11).

Wegener’s granulomatosis may mimic or overlap other vasculitides affecting the eye. Palmowski and coworkers report on a 46-year-old patient who presented with a picture consistent with Cogan’s syndrome with interstitial keratitis and vestibular–auditory dysfunction. This patient also had necrosis of the nasal septum, and the ultimate diagnosis was believed to be WG (12).

Wegener’s granulomatosis may be quiescent for long periods of time and then relapse, including in the ocular system. Piercey and Montanaro report on a patient with biopsy-proven WG (upper and lower respiratory tract) in remission for 18 years who developed a solitary nidus of orbital recurrence. This was successfully treated with cyclophosphamide (13).

Advances have been made in the laboratory, radiologic, and pathologic armamentarium used to diagnose WG. Many of the advancements in the serologic testing have been in the use and interpretation of the ANCA assay, which has become the primary diagnostic screening test for WG.

Edgar summarizes the utility of this indirect immunofluorescent test. There are two major staining patterns: cytoplasmic, or classic, ANCA (c-ANCA), whose target antigen is proteinase 3; and perinuclear ANCA, whose target antigen is myeloperoxidase. Other antigens also can give positive reactions. Although c-ANCA is largely associated with WG, whereas perinuclear ANCA is associated mainly with microscopic polyangiitis in the kidney, other diseases may cause a positive finding on ANCA assay. These include autoimmune hepatitis, Henoch-Schönlein purpura, ulcerative colitis, and malignancies (14).

Rao and colleagues prospectively studied 346 consecutive patients believed to have vasculitis based on the c-ANCA assay results. After excluding those with known WG and those who had been on noncorticosteroid immunosuppressive therapy before performing the c-ANCA assay, 212 met the study criteria. Of these, 14 (7%) had positive serologic findings for ANCA. Twenty-five patients met the 1990 American College of Rheumatology criteria for the diagnosis of WG. The overall sensitivity rate for WG was only 28%, yet the specificity rate was high (96%). Among the subset of 25 who met
American College of Rheumatology criteria, six were biopsy-positive, and five of these six (83%) had positive c-ANCA assay results. Thus, a negative finding on c-ANCA assay does not rule out clinical WG, yet a positive finding is highly specific for WG (15).

Rao and others also reviewed all relevant articles examining the utility of the c-ANCA assay as a diagnostic test for WG. The reported sensitivity rate of c-ANCA assay ranged from 34% to 92%, and the specificity rate from 88% to 100%. If all data were pooled, the overall sensitivity rate was 66%, and the specificity rate, 98%. If only active disease was examined, the pooled sensitivity rate was 91%, and selectivity rate, 99%. If the pooled data for patients with clinically inactive disease were examined, the sensitivity rate was 63%, and the specificity rate was 99.5%. Rao and others point out that data from the c-ANCA assay must be interpreted in the context of disease activity (16).

The clinical utility of this specificity in limited ocular disease is illustrated by the case reported by Soukiasian and colleagues (17). Their patient presented with a conjunctival nodule and scleritis; biopsy of the nodule suggested Wegener’s. When the ANCA assay finding was positive, the patient was successfully treated with trimethoprim–sulfamethoxazole (TS; see later), and the ANCA assay findings normalized.

Similarly, Yamashita and coworkers report on a patient who had bilateral exophthalmos for 9 months, believed to be caused by idiopathic orbital pseudotumor. When systemic signs were noted (microhematuria, purulent nasal discharge), an ANCA assay was performed and found to be elevated. The patient was specifically treated with cyclophosphamide and corticosteroids, and the inflammation resolved (18). Yamashita and others thus recommend that all patients with orbital pseudotumor undergo an ANCA assay.

Recent reports have dealt with the utility of ANCA as a marker for disease response to therapy. Power and colleagues report a series of eight patients with scleritis alone or scleritis and peripheral ulcerative keratitis. None had the diagnosis of WG before their evaluation. All eight remitted in response to oral cyclophosphamide therapy, with or without adjunctive corticosteroids. Five patients relapsed with treatment withdrawal; in four of these five (80%), the ANCA assay result had not normalized during therapy. The ANCA assay showed a significant rise prognosticating clinical relapse in only one of these five. All three patients who remained in remission continued to have a normal result on ANCA assay. Thus, in this series, if the ANCA level did not normalize with therapy, the patient with ocular manifestations of WG was more likely to relapse (19).

Gobel and associates studied another assay’s utility in diagnosing WG: the antineutrophil cytoplasmic antibody (ANCA) assay. Elevated ANCA assay levels were found in all patients with active WG but not in all of those who had positive c-ANCA. Elevated ANCA was seen in some WG patients with inactive disease, but no patient with active WG had a normal ANCA level. In general, patients about to enter remission would show a decrease in ANCA, and patients entering a relapse would demonstrate an elevation in ANCA. Thus, ANCA assay may be another useful assay in diagnosing WG and may be useful in predicting disease activity and response to therapy (20).

Provenzale and Allen retrospectively reviewed computed tomography (CT) and MR imaging scans of 15 patients with known WG and found abnormalities found in 7. These were dural thickening with enhancement (n = 3), infarcts (n = 2), hyperintense signal on T2 (n = 2), and abnormalities in the brain stem (n = 2). Dural thickening with enhancement (n = 3) is thought to represent granulomatous involvement of the dura. No case demonstrated extension into the CNS from contiguous orbital or sinus involvement. No patients showed evidence of CNS vasculitis (21).

Muhle and others reviewed the imaging findings of a subpopulation of WG patients (22). Of 121 patients with biopsy-proven WG, 12 had clinical orbital involvement. Of these, 10 underwent MR imaging scanning; 2 of these 10 also underwent a CT scan. They report that the MR imaging findings of orbital granuloma are low signal in T1 and T2 weighted spin echo sequences, with an inhomogeneous enhancement characteristic.

Nuclear medicine studies also have advanced diagnostic imaging capabilities. Roccarcello and others, using indium scans, studied 16 patients with rapidly progressive glomerulonephritis with arteritis and extensive crescent formation (23). Eight of these 16 were known to have WG. They found that significant accumulation of the tracer in the paranasal sinuses suggested that the cause of the glomerulonephritis was WG. This accumulation of indium was observed to reverse with therapy in some cases. They conclude that indium scan may prove to be a useful diagnostic tool in WG.

In contrast, in a limited experience, ocular ultrasound was not useful in identifying WG. Janknecht and colleagues used ultrasound in a patient with a sclerocochoroidal granuloma and could not differentiate the lesion from uveal melanoma (24). Histologic evaluation demonstrated that WG was the underlying process.

As with other vasculitides, the cornerstone of diagnosis of WG remains histopathologic examination. Matsubara and coworkers report on the utility of early nasal biopsy in the diagnosis of WG (25). They evaluated 11 patients with WG who had undergone nasal biopsy. The pathologic findings in this series were as follows: microabscess in vascular walls in 82%, leukocytoclastic capillaritis in 73%, fibrinoid necrosis in 45%, leukocytoclastic endovasculitis in 27%, palisading granuloma in 100%, microabscess in 91%, and diffuse granulomatous tissue in 82%.

Eight of these 11 patients (73%) went into remission; the remaining 3 (18%) died of their disease. Leukocytic vasculitis was more common in the fatal cases and predicted dissemination and a poor prognosis, whereas the specific form of leukocytoclastic endovasculitis was seen only in the fatal cases. The authors suggest that the
pathologic subtype may assist the treating clinician in selecting how aggressive a regimen will be employed.

The availability of such seminal information may prove to be useful for the clinician as new therapies for WG become available. The traditional therapy of cyclophosphamide and glucocorticosteroid is effective but is relatively toxic, and alternate therapies for those with less aggressive illness have been sought. Several articles report on some of these alternative strategies.

Le Thi Huong and others investigated the use of an alternate dosing strategy of cyclophosphamide (26). Fourteen consecutive patients with active WG received prednisone and monthly pulse cyclophosphamide. One patient died of sepsis related to leukopenia. Long-term remission was induced in 42%, and responders were more likely to have less extensive disease than were nonresponders. Side effects were common, although, aside from the one death, were mild.

Reinhold-Keller and colleagues looked at the results of therapy of initial-phase WG with TS (1920 mg/day) in 19 patients. Eleven of these 19 (58%) went into complete or partial remission with this therapy. The mean length of this remission was 43 months. Five (26%) of the remaining eight who did not respond had focal extension of their disease, whereas three (16%) developed generalized WG (27). This group also looked at the utility of this therapeutic regimen in 24 patients with generalized WG who had already received immunosuppressive therapy. Of the patients with generalized WG who received TS after standard therapy, 42% relapsed with a mean time to relapse of 13 months. In the group that received standard therapy and did not get TS, 29% relapsed after a mean duration of 22.5 months. Thus, in this study, TS was not a useful adjunct therapy for advanced disease and may be more useful in initial phases of WG.

Stegeman and others, in noting that respiratory infections have been reported to trigger relapses in WG, conducted a prospective study of TS at a dose of 1920 mg/day for 24 months to study if this would diminish the frequency of relapse in patients in whom remission had been induced. Eight of 41 (20%) patients had to stop TS because of side effects. Eighty-two percent of those receiving TS were in remission at 24 months, compared with 60% of the placebo group. There were no differences in ANCA titers between the two groups. They concluded that TS prevents relapses in WG (28).

Another alternate therapy for non-life-threatening WG has been reported by Sneller and coworkers. Weekly low-dose methotrexate and prednisone induced remission in 71% of their patients, with a median time to remission of 4.2 months and a median time to relapse of 29 months. Among the patients who relapsed, six of the eight (75%) who were retreated with the regimen had remission reinduced. The authors concluded that weekly low-dose methotrexate with prednisone is a reasonable alternate therapy in selected cases of non-life-threatening WG (29).

Person reports on the therapy of a case of WG with dapsone (30). This 75-year-old man had chronic nasal obstruction and several cutaneous nodules that pathologically showed granuloma lobular panniculitis. A subsequent nasal biopsy showed granulomatous vasculitis consistent with WG. Therapy with TS did not halt disease progression. Dapsone (which acts by inhibiting neutrophil myeloperoxidase and neutrophil chemotaxis), at a dose of 50 mg twice daily, controlled his clinical illness and normalized his sedimentation rate, and a maintenance dose of 25 mg daily maintained this remission.

Alternate therapies for severe disease unresponsive to cyclophosphamide and steroids have been reported. Georgana and associates treated a 52-year-old man, who had had a splenectomy, with severe WG that was refractory to this traditional therapy (31). He was initially stabilized with plasmapheresis and gamma globulin, and remission was successfully induced with cyclosporine.

In Europe, there is an experience with therapy of desensitized immunoglobulin to cyclophosphamide and steroids. Hagen and others treated five patients, who were unresponsive to or could not tolerate alkylating agents, with antithymocyte globulin. Four of five (80%) of patients responded, with side effects including labial herpes simplex and serum sickness (32).

Morgenstern and Pardo report a neurologic complication of therapy for WG (34). Their patient developed biopsy-proven progressive multifocal leukoencephalopathy after therapy with cyclophosphamide and prednisone. Withdrawal of immunosuppression led to neurologic recovery.

**Temporal Arteritis**

Temporal arteritis (TA), a giant cell arteritis, is the most common vasculitis likely to be encountered clinically by the ophthalmologist and neurologist. TA affects large- and medium-sized arteries, which have a well-defined elastic lamina. Temporal arteritis, is somewhat of a misnomer, since it is not limited to involvement of cranial arteries. Any arterial bed may be affected, although extracranial branches of the carotic arteries are the most commonly affected vessels. Ischemia from TA is rarely observed below the neck, with preferential involvement of the ophthalmic, posterior ciliary, superficial temporal, facial, occipital, and maxillary arteries. What these arteries have in common is a high elastic component in their media and adventitia (3).

Temporal arteritis is a common vasculitis and has well-reported clinical manifestations. Nonetheless, a few unusual clinical features have been described. Sonnenblick and colleagues report visual hallucinations (the Charles Bonnet syndrome) as the presenting sign of TA in an 87-year-old woman (35). The hallucinations were followed by headache and monocular visual loss.
After biopsy confirmed TA, the institution of corticosteroid therapy eliminated the hallucinations. Seven months later, the patient experienced a recrudescence of the visual hallucinations, which responded to an increase in the corticosteroid dose. Fineman and others report on a 77-year-old patient with TA whose presentation was a non-embolic branch retinal artery occlusion. Three weeks later, the patient developed ipsilateral ischemic optic neuropathy. Nassant and coworkers report an unusual presentation of TA, with bilateral orbital inflammation seen clinically and demonstrated on both CT and MR imaging scans. A temporal artery biopsy showed that TA was the source of the inflammation. Ruiz-Masera and colleagues describe a case of facial artery involvement in TA where the presenting sign was a submandibular mass.

There are cases of TA where it is difficult to differentiate between the polymyalgic onset of rheumatoid arthritis in the elderly and TA. Kassimos and others found that assays for serum cytidine deaminase may help to differentiate these two clinically similar disorders. They found that 36 of 40 (90%) patients with TA or polymyalgia rheumatica (PMR) demonstrated normal levels of cytidine deaminase (mean 8.64 U/mL), whereas in the 20 patients with polymyalgic rheumatoid arthritis the mean was 21.33 U/mL. This was statistically significant (p < 0.0001), and they concluded that the level of cytidine deaminase may therefore be a useful marker to differentiate polymyalgic rheumatoid arthritis from TA.

Several immunologic markers are being evaluated as to whether they are useful in understanding the pathogenesis of and in guiding rational therapy of TA. Liozon and associates prospectively studied 86 biopsy-proven TA patients and 50 controls to assess if antinuclear antibodies (ACA) were markers for disease activity. Before therapy, 50% of the TA cases and 8% of the controls were positive for ACA (36% had ACA-IgG, 17% had ACA-IgM). In this study, there was no association between the presence or level of ACA and ischemic ocular manifestations of TA. Corticosteroid therapy normalized ACA levels, and relapses were accompanied by an increase in ACA. Their conclusion was that the presence of ACA may be a marker for TA disease activity.

Chakravarty and associates evaluated ACA levels in 99 patients with PMR or TA. They found that among patients with a presentation of pure PMR, the finding of an elevated ACA at time of presentation carried a 4.82 relative risk for the development of TA. They also found that 35 (60%) of the patients presenting with TA with a high level of ACA at presentation developed severe vascular complications (defined as stroke or anterior ischemic optic neuropathy). No patient in their study who did not present as pure TA developed these ischemic vascular complications. They reasoned that an elevated ACA level in a patient presenting with TA may prognosticate for a more severe course.

Salvani and others performed a prospective study of 38 patients with TA or PMR. They studied levels of soluble interleukin-2 (sIL-2R) and CD8-positive cells assayed before the institution of therapy, 6 months into corticosteroid therapy, and at the patient's last visit. As opposed to controls, patients with active disease had higher sIL-2R and lower levels of CD8 cells. With therapy, erythrocyte sedimentation rate, C-reactive protein, and sIL-2R declined significantly. Despite 6 months of therapy, CD8 levels remained significantly lower than in controls, and sIL-2R was significantly higher than in controls. They found that if the percentage of CD8 cells after 6 months of therapy was more than one standard deviation below that found in controls, then the patients required significantly longer corticosteroid therapy, and concluded that reduced levels of CD8 cells at 6 months of therapy may identify a group with more severe disease.

Emilie and associates studied the production of serum interleukin-6 (IL-6) levels in patients with TA. They found that compared with controls, serum IL-6 levels are increased in patients with TA and fall with corticosteroid therapy. IL-6-producing cells were demonstrated in all layers of arteries affected, but were particularly rich in areas of the media that were in contact with the internal elastic lamina. In the media, they found that most of the IL-6-producing cells were macrophages, whereas in the intima, fibroblasts also were found to produce IL-6.

Roche and coworkers studied both IL-6 and tumor necrosis factor-alpha levels in patients with TA and PMR. They found that IL-6 was increased before therapy in both PMR and TA patients, whereas tumor necrosis factor-alpha was not. Corticosteroids rapidly reduced circulating IL-6 levels but did not diminish the increased local production of IL-6. They also found that changes in circulating IL-6 levels varied in parallel with alterations in the clinical status, and that withdrawal of corticosteroids led to increased IL-6 levels. They believed that this suggested that IL-6 contributes to disease manifestations, and that monitoring IL-6 may play a role in guiding the dose of corticosteroids in these patients.

Weyand and Goroszy conclude that TA is likely a disease where the vessels carry an as-yet-unidentified antigenic target. Selected helper T cells migrate to lesions where cytokines are produced and macrophages are activated. They believe that a genetic risk factor includes the expression of a region of the HLA-DR molecule.

Kraft and coworkers report the promise of color Doppler ultrasound as a possible new tool for identifying patients with TA. They studied 10 patients with TA and 8 with PMR, as well as 23 controls, with high-resolution ultrasound. The size of the temporal artery lumen was assessed, as was blood flow velocity. They found that there was a typical hypoechoic halo around the perfused lumen of stenotic or thrombosed superficial temporal arteries. This halo was not seen in controls or in the arteries of PMR patients. Furthermore, they said that the halo disappeared with 10 to 14 days of corticosteroid therapy.

Dautzenberg has described a case of dementia where SPECT scanning improved with prednisone therapy.
The patient was an 81-year-old woman who underwent SPECT scanning to evaluate an acute dementia evolving over a few weeks. This was believed clinically to be vascular, but the initial SPECT scanning suggested Alzheimer's dementia as the underlying etiology, with poor perfusion in both parietal regions. Since this patient was previously known to have had TA, she was treated with prednisone; the dementia partially reversed, and the right parietal perfusion was seen to improve on SPECT scan 1 year into her therapy.

The limitations of the current therapy of TA are well represented by the case reported by Rauscher and Rismanada, a 74-year-old woman with TA who presented with 2 weeks of diplopia and 4 weeks of temporal headache and myalgia, with recent weight loss. The Westergren erythrocyte sedimentation rate was 115 mm/h, and 80 mg of prednisone daily was begun. Results from a temporal artery biopsy were positive. The diplopia and constitutional symptoms resolved within 1 week of therapy, and 2 weeks into therapy the sedimentation rate was 31 mm/h. Despite this clinical response, 1 week later, the patient had ischemic optic neuropathy left eye (OS) while still on 80 mg daily of prednisone. At this point she was free of constitutional symptoms and her sedimentation rate was 15 mm/h (48).

The two large concerns with the standard protracted corticosteroid therapy for TA are as follows:

1. How should patients be treated who break through or are unresponsive to corticosteroid therapy?
2. Is there a way to avoid corticosteroid-induced complications of therapy?

Currently, there is no proven effective alternate regimen to corticosteroid therapy. Thus, the thrust of most of the investigations of the therapy of TA center around whether there are safe alternate therapies employing adjunct agents to long-term corticosteroids, or if there are regimens employing other steroid-sparing agents that allow for a shorter duration of or lesser total dose of corticosteroid therapy.

Hernandez-Garcia and others treated 11 patients with newly diagnosed TA with an initial high dose of prednisone and rapidly tapered the dose. The patients also received weekly oral methotrexate for 2 years. They found that it took a mean of 14 weeks to get down to a dose of 10 mg of prednisone daily, and 30 weeks until withdrawal of the corticosteroid was possible. While on this regimen, two patients relapsed, and five developed side effects of corticosteroids, whereas no complications of methotrexate were seen. They believed that their small series showed that methotrexate might be a safe and useful therapeutic modality in TA (49).

Kumar and others report a 65-year-old man with Takayasu's arteritis who had painless progressive visual loss OD over 1 year. He also had transient bilateral visual obscuration lasting up to a few minutes. The patient was light perception OD with a dense cataract preventing inspection of the fundus. The acuity in the left eye was 6/24 OS. Dilated episcleral and conjunctival vessels were seen OU, as was bilateral iris neovascularization. The left fundus demonstrated mild temporal pallor with a few anastomotic loops on the disc surface. “Boxcarring” was seen in large arteries, with venous dilation and tortuosity. The fluorescein angiogram showed a prolonged arm to retina time, delayed choroidal filling, and patchy hypofluorescence of the disc. There was early cystoid macular edema, but no disc neovascularization. The authors commented that it was unusual to have such severe anterior segment ischemia without more advanced fundus findings (52).

Similar to the study performed by Kraft and others in TA (46), Raninen and colleagues looked at the utility of B mode ultrasonography as an aid in the diagnosis of Takayasu's arteritis (53). They measured total wall, intimal plus medial, and adventitial thickness of the common carotid, subclavian, and common femoral arteries, as well as the abdominal aorta. They found that in their 16 patients, compared with their control group, all vessels other than the common femoral showed significant increases in total wall and intimal plus medial thickness.
SYSTEMIC LUPUS ERYTHEMATOSUS

Reviewing all progress in the understanding of and therapy of SLE is beyond the scope of this review. Here we concentrate on a few specific presentations and points regarding neurologic and ophthalmic involvement in SLE.

Ahmadieh and others recently reported in this journal on an 11-year-old girl diagnosed with systemic lupus erythematosus (SLE) who, 3 months after diagnosis, developed bilateral optic neuropathy with retrobulbar pain on ocular rotation. The initial visual acuity was light perception OU. Therapy with oral prednisolone (4 mg/kg/day) led only to recovery of counting fingers OU. Whether this patient exhibited APA is not reported in the article. The authors point out that optic neuritis in SLE in children has had a poor outcome in the few cases reported (54).

The presence or absence of neurologic disease at the time of diagnosis of SLE and during its course are markers for disease survival. Golstein and others studied 92 consecutively diagnosed patients with SLE (24 of whom had neurologic or ophthalmic disease) to see if the presence of APA correlated with neurologic and ophthalmic involvement. The most common neurologic findings were stroke or transischemic attack (n = 9), psychotic delirium (n = 9), and seizures (n = 6). The five ophthalmic manifestation seen in the series were central retinal artery occlusion (n = 4) and central retinal vein occlusion (n = 1).

Thirty-two percent of patients without neurologic or ophthalmic illness were positive for APA, whereas 15/24 (63%) of those with such disease were APA-positive (p < 0.01). In 13/15 cases (87%), the detection of APA antedated the neurologic/ophthalmic sign. There was no correlation between having a positive APA finding and the specific type of neurologic/ophthalmic manifestation. Golstein and coworkers conclude that a positive APA finding is a risk factor for neurologic and ophthalmic disease in SLE. They do not recommend any preventative therapy for the SLE patient found to harbor APA who has not yet had a neurologic/ophthalmic complication (55).

Seaman and colleagues looked at the significance of APA in SLE in children. Twenty-nine patients with SLE diagnosed in childhood were examined, with the presence of APA defined as demonstrating either a false-positive VDRL, the presence of lupus anticoagulant, or ACA-IgG or ACA-IgM. They found that 65% of their patients demonstrated at least one of these three abnormalities, with a false-positive VDRL in 11/28 (39%), lupus anticoagulant in 16/26 (42%), and anticardiolipin antibodies in 18/27 (67%). In this series, thrombotic events were correlated with the presence of anticardiolipin antibodies (56).

Denburg and others recently reported on the relation of neurologic involvement in SLE and the development of guidelines for therapy (57). Denburg and colleagues believe that prevailing evidence supports that this is a disease process mediated by autoantibodies evident in the serum and the cerebrospinal fluid. These autoantibodies may effect CNS involvement by various mechanisms. These include antibody-dependent cytotoxicity, which may cause cell death or demyelination, or by interference with cell-cell communication. They point out that there is a body of evidence linking some of these potential mechanisms to specific neurologic presentations in SLE. Thus, the presence of APA in SLE patients is linked to focal neurologic deficits, whereas producing antineuronal antibodies tends to be associated with diffuse neurologic or neuropsychiatric involvement, and having antibodies directed against ribosomal P proteins is associated with psychosis and depression. Their conclusion is that the treatment of neurologic involvement of SLE should be tailored to its presumed etiopathogenesis in the individual patient. Thus, neurologic lupus that is thrombotic is treated using known therapeutic regimens applicable in stroke, such as warfarin, whereas neurologic lupus that is believed to be mediated through autoantibodies is treated with therapeutic agents used in autoimmune disease models such as myasthenia, including immunosuppressants.

HYPERCOAGULABLE STATES

Although local anatomic risk factors have been well described in the pathogenesis of nonarteritic ischemic optic neuropathy, it is not always clear when an investigation for other potentially important etiologic factors should be undertaken. Hypercoagulability and prethrombotic conditions have long been associated with the development of spontaneous venous thrombosis, but the association of these conditions with arterial thrombosis has been recognized only recently (58–61). Acheson and Sanders (62) describe coagulation abnormalities in seven patients with nonarteritic ischemic optic neuropathy over a 2-year period. Four patients had deficiencies in the anticoagulant proteins C and S as well as antithrombin III, two had antiphospholipid antibody syndromes, and one patient had reduced levels of physiologic tissue plasminogen activator. Six of these seven patients had bilateral ischemic optic neuropathy, and four had experienced recurrent episodes in the same eye. Additionally, two of the seven patients had presented before the age of 30 years.

Hypercoagulability may be divided into two categories based on whether identifiable alterations exist in the hemostatic pathway. Patients who have identifiable abnormalities then can be divided into subgroups, depending on the site of alteration (i.e., blood [cellular components] serum [anticoagulant and fibrinolytic enzymes], presence of lupus anticoagulants or antiphospholipid antibodies), or the vascular endothelium). These can be further subdivided, depending on whether the abnormalities are congenital or acquired. Until 1994, the most common identifiable disorders of hemostasis in patients with spontaneous venous and arterial thrombotic events were deficiencies in antithrombin III, protein C, and protein S (62,63). Congenital protein C deficiency accounts for up to 10% of all patients with deep venous thrombo-
sis or pulmonary embolism, and antithrombin III deficiency accounts for 3% to 8% of these patients. Protein S deficiency may account for 5% to 10% of unexplained venous thromboses in patients younger than 45 years of age (64). Interestingly, in a study of 40 cases of cerebral venous thrombosis in adults from Saudi Arabia, the most common etiology was Behcet's disease, which occurred in 25% of patients. Protein S and antithrombin III deficiency (12.5%) and APA (10%) were other common causes considered as sources for the thromboses (65). Unfortunately, most investigations for hypercoagulable states were unable to define an etiology in approximately 70% of cases. Certainly, labeling most as idiopathic is not useful from a therapeutic or a genetic pathophysiologic standpoint. However, in 1993, Dahlbeck and associates (66) made the seminal discovery of resistance to activated protein C, which now is believed to account for most cases of familial thrombophilia. Such resistance to protein C was found to be caused by an R506Q mutation in the gene coding for factor V, which was termed factor V Leiden (67). As a result of this mutation, factor V cannot be neutralized by protein C on activation by thrombin–thrombomodulin complex, leading to excess factor V activity and a prethrombotic state (Fig. 1).

The discovery of activated protein C resistance not only accounts for a substantial percentage of hereditary thrombotic disorders, but also may provide an explanation for the etiology of hypercoagulability in other conditions in which the mechanisms of thrombosis have been previously unknown. For example, patients who are homozygous for homocystinuria have only a one in three probability of developing a thrombotic event. This implies that there may be additional factors that are necessary for the development of thrombosis. Mandel and others demonstrated that coexistence of the factor V Leiden mutation in 7 of 11 patients with homocystinuria was associated with thrombotic events in 6 of these 7 patients (68). The only patient with both homocystinuria and factor V Leiden mutation who did not develop thrombosis had received warfarin therapy since birth. The four homocystinuria patients without the factor V Leiden mutation have yet to develop thrombosis.

Despite the unequivocal importance of activated protein C resistance as a cause of hypercoagulability, knowledge of this condition has not been well disseminated throughout the medical community as would be expected, although 37 of the 115 articles published since its discovery have been written in journals typically read by primary care physicians. Additionally, only six of the articles were published in journals read by pathologists (69). This may account for the lack of awareness of this condition among community pathologists who are potentially invaluable in assisting the treating physician in selecting the appropriate laboratory studies for a hypercoagulability workup. This was well illustrated in a study conducted at the University of Utah that was designed to establish prevalence data regarding ordering of various diagnostic laboratory tests by community and university physicians seeking to identify a specific thrombotic disorder. Testing for other inherited thrombotic disorders such as antithrombin III, protein C, and protein S deficiency occurred at a rate sixfold greater than that for activated protein C resistance. Furthermore, 37% of the specimens collected for evaluation for activated protein C deficiency were not evaluable because of concomitant anticoagulation therapy (69). Resistance to activated protein C was identified by measuring the activated partial thromboplastin time (aPTT) with added activated protein C, and comparing the resultant value to the aPTT without addition of activated protein C. In normal individuals, addition of activated protein C prolongs the aPTT by two to three and a half times. A ratio of less than 2.0 is presumptive evidence for activated protein C resistance (70). Since heparin anticoagulation prolongs the aPTT, specimens sent for determination of activated protein C resistance after heparin therapy was initiated could not be assayed. These statistics underscore the lack of aware-

![FIG. 1. Role of protein C in modulation of thrombosis.](image-url)
ness as well as the lack of understanding of the laboratory assay used to diagnose this disorder.

In summary, activated protein C resistance has emerged as the leading cause of inherited thrombophilia, and therefore appropriate laboratory studies to identify this condition should be performed when evaluating patients with recurrent or unusual thromboses or thromboembolism.

**Antiphospholipid Antibodies**

Central nervous system disease in SLE patients is well known to be associated with the presence of APA (71). However, the prevalence rate of CNS disease in SLE patients is variable, with reports ranging from 18% to 70% (72). This variability likely results from a lack of standardized methods to define subtle clinical CNS manifestations. Such wide variability in reported prevalence leads to conflicting reports with respect to its association with other features of SLE, namely the prevalence of APA antibodies. If more specific definitions of CNS disease are outlined, then prevalence rates of its associated features can be obtained more consistently. Toubi and others identified 96 of 340 unselected patients at a lupus clinic with CNS manifestations, including 55 with transient ischemic attacks or strokes, 24 with epilepsy, and 12 with psychiatric disorders, and compared them with a control group of 100 patients without CNS or thromboembolic manifestations in terms of APA positivity and presence of other clinical and serologic markers of lupus disease activity (73). Patients with migraine or cognitive disorders were excluded. Overall, 55% of the patients with CNS manifestations were positive for APA compared with 20% in SLE control patients. Additionally, only 44% of patients with CNS findings had clinical and serologic findings consistent with globally increased lupus disease activity, and the remaining 56% were inactive.

Serologic positivity for APA was strongly associated with SLE inactivity. Of the 53 patients who underwent MR imaging evaluation, 33 had changes consistent with vasculopathy and 26/33 had positive findings on antiphospholipid antibody serologic study. Only 8/33 patients with normal results on MR imaging scans had positive APA. In summary, the study demonstrates and confirms that a strong association exists between positive APA serologic findings and CNS disease in SLE patients, and that abnormal results on MR imaging scans highly correlate with positive APA antibodies in patients with a restricted definition of CNS lupus. Additionally, CNS disease can occur in the absence of other evidence of lupus disease activity.

Focal cerebral infarction is the most common manifestation of arterial thrombosis in patients with the antiphospholipid syndrome (74). However, the prognosis, and the clinical, serologic, and other laboratory features require clarification. Levine and colleagues studied 81 patients consecutively with APA, who, over a 7-year period, developed cerebral thrombo-occlusive events (75). Patients with the highest titers of anticardiolipin antibody had the shortest times to ischemic occlusive events. The average age was 10 years younger than the average stroke patient, and women were more often affected than men. Additionally, over 50% of patients had more than one recurrent occlusive event, usually occurring within 1 year of follow-up.

The presence of APA in pathologic conditions other than stroke and recurrent fetal loss has led to the emergence of studies of prevalence of these antibodies and their potential role in the pathogenesis of other neurologic and nonneurologic conditions. Although, several reports (76–79) indicate a possible association and perhaps a pathogenic role in patients with migraine, these reports have not been substantiated by investigations on patients with migraine. Silvestrini and others, however, suggest that patients with migraine and APA may represent a specific subset of patients with migraine (80). In a study of 16 patients with migrainous stroke without other known causes of infarction, 6 of these patients were positive for the presence of APA antibodies. Additionally, those with positive serologic results had fewer risk factors for stroke than those without positive serologic evidence, thus indicating a possible causal or influential role for APA in the development of migrainous stroke.

Apropos to our earlier discussion regarding APA in other disease states is a case report of a patient with type 1 diabetes mellitus who presented with a central retinal artery occlusion and was found to have positive serologic results for anticardiolipin antibodies (81). Since patients with type 1 diabetes generally are believed to have developed diabetes on the basis of an autoimmune process leading to insulin and subsequent loss of B cells of the pancreas, it is not surprising that ACA antibodies may coexist, suggesting a more generalized disturbance of the immune system. The appearance of ACA antibodies has been related in two experimental models of diabetes insulinitis (82,83). This implies that development of thrombotic events in patients with type 1 diabetes may be partly related to the presence of ACA antibodies.

Until now we have focused on the complications related to APA through their effects on the coagulation pathway. However, Orefice and others (84) report a case of benign intracranial hypertension in a patient with primary antiphospholipid syndrome and no evidence of cerebral sinus thrombosis. Benign intracranial hypertension in patients with SLE often results from cerebral sinus thrombosis with impairment of CSF outflow. The only abnormal manifestations in this patient were high titers of APA and lupus anticoagulant.

Despite the numerous reports attempting to pathogenetically link various neurologic disorders with the presence of APA, caution must be exercised before attributing causal roles to these antibodies. Definitive pathophysiologic data have not been attained. Moreover, especially in disorders with other existing immunologic derangements, the presence of these antibodies may merely reflect a biological epiphenomenon and therefore are causally unrelated to the underlying disorder in question.

**Fig. 2.** Intrinsic and extrinsic coagulation pathways.

**Fig. 3.** Role of antithrombin III (AT) and heparin cofactor II in modulation of thrombosis.
LABORATORY EVALUATION OF HYPERCOAGULABLE PATIENTS

Once a prethrombotic state is suspected, systematic evaluation of the hemostatic and thrombotic pathways should be undertaken. The initial workup begins with a thorough history and physical examination followed by standard global tests of hemostasis such as platelet count, bleeding time, and measurements of the intrinsic and extrinsic clotting pathways (aPTT and prothrombin time; Fig. 2). Abnormalities in these initial laboratory tests should direct the ordering physician toward appropriate confirmatory tests to arrive at a specific diagnosis. However, it is more likely that in most cases of suspected prethrombotic states, the initial screening laboratory evaluation is within normal limits. Based on our previous discussion of congenital hypercoagulable states, laboratory assay for activated protein C resistance should be the next step. It is important that the blood sample be obtained before initiating anticoagulation. If this test result is negative, then the next step should be evaluation for anticoagulant deficiencies such as antithrombin III, protein C, and protein S. Often, however, since the range of normal is wide for each of these anticoagulants and minor deficiencies may be clinically significant, it is imperative that functional assays also be performed. Additionally, there may be existing conditions that interfere with determination of these functional assays, leading to false measurements of their activity. For example, heparin cofactor II (HC-II) is a naturally occurring anticoagulant that inhibits thrombin. Because HC-II inhibits one sixth of the amount of thrombin inhibited by antithrombin III, patients with minor reductions in functional or antigenic antithrombin III may not be detected, leading to an overestimation of its activity by 5% to 10% (Fig. 3). With this in mind, Demers and colleagues developed a new assay that uses factor Xa inhibition to determine functional antithrombin III activity. Factor Xa is not inhibited by HC-II, and thus patients with borderline antithrombin III activity can be appropriately identified.

Aside from measurements of anticoagulant deficiencies, serum markers reflecting increased coagulative activity may be useful in determining the nature of the hypercoagulable state. During the early stages of blood coagulation, activated protein C may appear in the circulation when subcoagulant amounts of thrombin are generated. Activated protein C may complex with alpha-1 antitrypsin, which has a longer half-life than activated protein C-antithrombin II complex. Increased amounts of these complexes reflect a stimulated coagulation pathway. Since the former complex has a longer half-life, it is more easily detected at an early stage of coagulation and is a sensitive marker of increased activity of the coagulation process, and therefore is a useful marker in prethrombotic states.

Evaluation for the presence of the lupus anticoagulant or other antiphospholipid antibodies begins with mea-
measurement of the aPTT. An elevated PTT is suggestive but not diagnostic of the presence of the lupus anticoagulant. A mixing study (using the patient’s serum mixed with normal control serum) is necessary. If this mixture results in normalization of the PTT, then this eliminates the presence of a lupus anticoagulant as the cause for PTT elevation and is implicit evidence for factor deficiency. Factor XII deficiency (Hageman factor) may lead to elevation of the PTT with a thrombotic tendency rather than a hemorrhagic diathesis, as in other factor deficiency states, as a result of interruption of the fibrinolytic pathway (Fig. 4). Factor XII is necessary in the activation of plasminogen to plasmin through its catalytic effect in activating plasminogen proactivator to plasminogen and conversion of prekallikrein to kallikrein. Conversely, a normal PTT value does not rule out the presence of a circulating anticoagulant, since the concentration of these antibodies may not be in sufficiently high titers to result in prolongation of the PTT, but yet may be a clinically significant cause of thrombosis. Dilution of phospholipid by using kaolin (kaolin clotting time) increases the sensitivity of the assay. The most sensitive phospholipid by using kaolin (kaolin clotting time) is Russell’s viper venom time.

REFERENCES


