Contents

219 The History of NANOS
Thomas J. Carlow

222 Lymphatic Capillaries in the Meninges of the Human Optic Nerve
H. Esriel Killer, Hubert R. Laeng, and Peter Groscurth

229 Opsoclonus in a Patient With Cerebellar Dysfunction
Maurizio Versino, Andrea Mascolo, Giovanni Piccolo, Roberto Alloni, and Vittorio Cosi

232 Toxic Optic Neuropathy After Concomitant Use of Melatonin, Zoloft, and a High-Protein Diet
Norman L. Lehman and Lenworth N. Johnson

235 Optic Nerve Enhancement on Magnetic Resonance Imaging in Arteritic Ischemic Optic Neuropathy
Andrew G. Lee, Eric R. Eggenberger, David I. Kaufman, and Carlos Manrique

238 Optic Nerve Enhancement on Orbital Magnetic Resonance Imaging in Leber's Hereditary Optic Neuropathy
Michael S. Vaphiades and Nancy J. Newman

240 Cat-Scratch Disease Presenting as Neuroretinitis and Peripheral Facial Palsy
P. Keith Thompson, Michael S. Vaphiades, and Michael Saccanette

242 Divergence Paresis: A Nonlocalizing Cause of Diplopia
Frederick E. Lepore

(continued on next page)
Ophthalmoplegia Associated With the Anti-Ri Antibody
Richard Ohmer, Karl C. Golnik, Arthur I. Richards, and Gregory S. Kosmorsky

Arachnoid Cyst of the Cavernous Sinus Resulting in Third Nerve Palsy
Dai Barr, Mark J. Kupersmith, Richard Pinto, and Roger Turbin

Microvascular Cranial Nerve Palsies in an Arabic Population
Mona al Saleh and Thomas M. Bosley

Intracranial Fatigable Ptosis
Yi-Feng Kao, Min-Yu Lan, Min-Shon Chou, and Wei-Hsi Chen

Literature Abstracts—Europe

Book Reviews

1999 Annual Update of Systemic Disease: Emerging and Re-emerging Infections (Part I)
Larry P. Frohman and Paul Lama

Acknowledgement from the Editor

Author Index

Subject Index
The History of NANOS

Thomas J. Carlow, M.D.

Inspired by the fever pitch atmosphere of the yearly Bascom-Palmer Eye Institute neuro-ophthalmology course and teaching enthusiasm of its faculty (Bob Daroff, Noble David, Lou Dell’Osso, Joel Glaser, Ed Norton, J. Lawton Smith, and Todd Troost), a southwestern “clone” was conceived by a young assistant professor of neurology, and sponsored by the Neurology Department at the University of New Mexico in Albuquerque. The initial 1975 Santa Fe program was such a success that the course became a yearly event. The inaugural faculty included Joe Cannon, Tom Carlow, Bob Daroff, Joel Glaser, and Bill Hoyt, with 156 registrants in attendance. Joe Bicknell, Chair of Neurology at the University of New Mexico, and Norman Schatz joined the teaching group to lecture in 1976.

The annual course quickly grew into a symposium for neuro-ophthalmologists. The fledgling organization adopted policies to attract new members, gradually from all parts of the United States and Canada. Once a neuro-ophthalmologist accepted an invitation to lecture, he or she typically returned, enthusiastically accompanied by friends and fellows. The list of neuro-ophthalmologists initially lecturing in the first ten years clearly demonstrates how important and successful this policy was for the subsequent growth of organized neuro-ophthalmology. Nancy M. Newman (CA) lectured in 1977; Shirley Wray in 1978; Henry Van Dyke, Bruce Wilson, and Brian Younge in 1979; Walter Cobbs, James Corbett, Lou Dell’Osso, Carl Ellenberger, Jack Kennerdall, George Sanborn, Peter Savino, Stan Thompson, Jon Wiggsfater, and David Zuel in 1981; Terry Cox, Noble David, Jack Selhorst, and Jim Sharpe in 1982; Roy Beck, Jim Goodwin, Steve Johnson, Mark Kuper-smith, Gerry Maithland, Tom Shults, Craig Smith, and Bob Spector in 1983; with Steven Newman (baby sister not until 1990) and Bob Sergott rounding out our tenth year in 1984. Membership and participation in our yearly symposia and organizational activities continue to flourish and grow with the addition of lecturers from all regions of North America and the world.

In 1978, the first formal non-neuro-ophthalmologist guest speaker was A. Earl Walker, emeritus professor of neurosurgery, from Johns Hopkins. Dr. Walker, a colleague of Frank B. Walsh at Johns Hopkins, had retired to New Mexico, and kindly accepted an invitation to participate. His lecture was titled “Pupil in Coma and Cerebral Death.” Thus began a tradition of superb, informative, and world-class guest speakers that has continued for more than two decades.

The University of New Mexico formally established a Department of Continuing Medical Education in 1979 and requested a surcharge for any program to be held under its auspices. Because all collected funds had always been spent to enhance the course, this policy prompted a transfer of all course fiduciary responsibility outside of the University of New Mexico and necessitated the formation of a society with Articles of Incorporation and Bylaws. The Rocky Mountain Neuro-Ophthalmology Course became The Rocky Mountain Neuro-Ophthalmology Society and was officially incorporated as a nonprofit organization on February 11, 1980 with 132 members. Suddenly, we had limited funds and no administrative infrastructure. Susan Carlow “volunteered” to assist with the yearly meeting. Little did she or the Society comprehend how the North American Neuro-Ophthalmology Society (NANOS) would grow exponentially and come to occupy such a significant component of her life.

NANOS has instituted several important and prestigious awards during the past 25 years. The first Resident Fellowship Award was won by David Zackon in 1983 for his paper titled “Vertical Supranuclear Gaze Palsy and Intrathoracic Carcinoid Tumor.” John Kerrison received the 17th award for his poster titled “Congenital Motor Nystagmus Linked to Xq26-q27” at our Snowmass, Colorado 1999 meeting. NANOS received its first endowment to sponsor a Young Investigator Award. This award was designed to encourage basic or clinical research in neuro-ophthalmology. It is granted after a review of a developing neuro-ophthalmic investigator’s total body of work and acceptance of a new research manuscript. Leonard Levin received the first Young Investigator Award in 1997, Jason Barton the second in 1998, and most recently, Wolf Lagnée in 1999.
After much discussion, the Rocky Mountain Neuro-Ophthalmology Society voted to change its name to the North American Neuro-Ophthalmology Society in 1986 at our Whistler meeting, thus recognizing that we had grown from primarily a national to an international society. By 1987, NANOS had 240 members from 46 of the 50 United States, most Canadian provinces, Australia, and England.

Significant dialogue, to make the yearly meeting accessible to adherents of both a winter and sun-soaked atmosphere, resulted in a change from our prototypic mountainside locale. In 1989, NANOS first ventured out of the Rocky Mountains to then hurricane-ravaged Cancun, Mexico. Our site selection committee now chooses two winter/ski venues for every sun/beach resort. This policy has provided an opportunity for all to enjoy the Rocky Mountains and, at regular intervals, warm weather sites in conjunction with our outstanding, informative scientific sessions.

In 1988, Roy Beck proposed that we sponsor a symposium at the American Academy of Ophthalmology (AAO). The first NANOS-AAO symposium was subsequently held in New Orleans in 1989. The broad subject of diplopia was presented under the aegis of Tom Carlow, and Peter Savino. This year will mark the 11th year of joint symposium sponsorship with the AAO. Barrett Katz and Alfredo Sadun are the current co-moderators. The topic to be addressed is: "A Medical-Legal Primer for Neuro-Ophthalmology: Common Traps, and How to Avoid Them." Attendance continues to soar. Last year there were more than 1000 physicians and paramedical personnel in the audience, with only standing room available.

At Stanley Thompson's suggestion, we had our inaugural poster session at Park City, Utah in 1991. It was an obvious success and has become an essential component of our yearly meeting. The Snowmass, Colorado 1999 session had 73 posters with discussion extending over 3 hours. It was accompanied by a festive Chinese box dinner.

Nineteen hundred ninety-one was a momentous and in some ways tumultuous year for organized neuro-ophthalmology. The Frank B. Walsh Society had incorporated, providing NANOS and the Frank B. Walsh Society the opportunity to consider a formal corporate merger. First merger discussions were held in Salt Lake City after the Frank B. Walsh meeting and then, within the same week, at the NANOS Park City meeting. Ultimately, 98% of both societies endorsed a merger in November 1991. New Bylaws were approved by NANOS at our 1992 Rancho Bernardo, California business meeting, and then by the Frank B. Walsh Society at the Los Angeles meeting that followed. The legal document completing the union was signed by Tom Carlow and Bob Daroff for NANOS, and Bill Hoyt and Dave Knox for the Frank B. Walsh Society at the Williamsburg, Virginia, International Neuro-Ophthalmology Society Meeting on June 29, 1992.

Todd Troost, as NANOS publication's committee chair, began negotiations for a NANOS sponsored Journal of Neuro-Ophthalmology in 1992. His effort was re-

FIG. 1. NANOS 1999 Distinguished Service Awardees (David Knox, Robert Daroff, William F. Hoyt, Susan Carlow, Joel Giaser, and Thomas Carlow).
awarded when a contract was signed with Raven Press in January 1994 to assume the role of the official journal of NANOS. Ron Burde and J. Lawton Smith were joint editors for the first year. Ron Burde, along with his editorial board, has directed and developed the *Journal of Neuro-Ophthalmology* into an extremely valuable and indispensable component of NANOS.

NANOS was officially launched onto the information superhighway in 1995 through the efforts of Preston Calvert and Todd Troost, with the establishment of its own web page. Our Society now has a totally new and powerful dimension to explore and vehicle through which to communicate. NANOS E-mail discussion groups, as listed and described in this year’s syllabus, have expanded to currently include: NANOSLTR, NANOSNET, NANOSBIZ, PLACECTR, NANOS HOME PAGE, and an ARCHIVES PAGE.

A particular personal high point, in the organizational development of NANOS, has been to observe the dedication and commitment that each subsequent NANOS president has brought to that office. Jim Sharpe, Steve Feldon, Jon Wirtschafter, and currently Jack Selhorst have all contributed not only significant time, expertise, and effort, but have imbued NANOS with their own unique personality, attributes, and interests. They have all served NANOS with distinction and each can be extremely proud of their contribution to our subspecialty.

NANOS now has 375 members in the United States, Canada, Australia, Argentina, Belgium, China, England, Germany, Israel, Italy, Japan, Scotland, Switzerland, Taiwan, and Thailand. Our organization now represents the subspecialty of neuro-ophthalmology in a truly global sense.

The NANOS Board recently developed a distinguished service award to be given to members of NANOS who have significantly advanced the development, education, and organization of neuro-ophthalmology during an extended period. The first Irish crystal awards were given to Susan Carlow, Tom Carlow, Robert Daroff, Joel Glaser, William Hoyt, and Norman Schatz at our 25TH Anniversary meeting in Snowmass, Colorado on St. Patrick’s Day, March 17, 1999 (Fig. 1).

Several fundamental NANOS principles, not inscribed in our Bylaws, have existed since its conception: learning neuro-ophthalmology can and should be fun; learning neuro-ophthalmology can be accomplished in a relaxed and pleasant environment; during the annual meeting, time should be made available for members to socially interact with colleagues and their families. During the past 25 years, NANOS has maintained and fostered these principles. The scientific sessions have consistently been tremendous and exceptional. Participants have all shared important moments with colleagues and their families from the peaks of the Canadian Rockies to the top of the pyramids at Chichen Itza in Mexico, and from Orlando, Florida to Rancho Bernardo, California. These opportunities would have been impossible without abiding to the above fundamental guiding precepts.

Because NANOS now represents organized neuro-ophthalmology, it must protect the moral imperatives of our times while accepting the educational, political, and economic responsibilities that accompany its mission. As we enter the 21st century, NANOS must promote excellence in patient care, become a leader in innovative medical education, support neuro-ophthalmic research, investigate new modalities for our membership to communicate, and continue to represent the ideals of medicine that originally enticed us into our unique profession.

**Addendum from the Editor**

A moment in time grabbed by individuals with foresight has produced something for which we should be proud. Thanks to the Executive Vice President and founder of NANOS, Tom Carlow, and special thanks to the winners of the initial NANOS Distinguished Service Award.
Lymphatic Capillaries in the Meninges of the Human Optic Nerve

H. Esriel Killer, M.D., Hubert R. Laeng, M.D., and Peter Groscurth, M.D.

Objective: Although many anatomic studies of the orbit and the optic nerve have been performed, lymphatic capillaries in the dura of the human optic nerve have never been reported. This study was performed to determine whether or not lymphatic capillaries are present in the dura of the human optic nerve.

Materials and Methods: This postmortem study was carried out in seven subjects without ocular disease. The subjects were obtained no later than 6 hours after death, following qualified consent for autopsies. The dura of the human optic nerve was studied with light microscopy, scanning electron microscopy, and transmission electron microscopy. In some cases, india ink was injected into the subarachnoid space as a marker.

Results: Lymphatic capillaries in the dura of the human optic nerve were morphologically demonstrated with histological criteria (fenestrated endothelium, lack of a basal membrane, and absence of blood cells in the lumen of the vessels). The highest concentration of lymphatic capillaries was found in the bulbar part of the dura behind the ocular globe. Using light microscopy and transmission electron microscopy, ink was seen within the lumen of the lymphatic capillaries. The dura itself was not stained with the marker.

Conclusion: The presence of lymphatic capillaries in the dura of the human optic nerve was demonstrated with light microscopy, transmission electron microscopy, and scanning electron microscopy.

Key Words: Cerebrospinal fluid papilledema—Lymphatic channels—Optic nerve meninges—Subarachnoid space.

The optic nerve (ON), a white matter tract of the central nervous system (CNS), extends from the cranial cavity through the optic foramen and into the orbit. The ON, an integral part of the CNS, bears an envelope of meningotheial cells and is surrounded by cerebrospinal fluid (CSF). The subarachnoid space (SAS) is lined with a fenestrated layer of meningotheial cells known as the neurothelium. The connective tissue of the meninges contains collagen fibrils and elastic fibers (1,5,8,21,32). It also harbors a dense network of arteries, veins, and unmyelinated nerves (5,8). The arachnoid villi is considered to be the major site of CSF absorption (15,16). Other sites and mechanisms of CSF absorption have been proposed in the literature (5,14,23,24). Schwalbe was the first author to suggest that CSF drainage into lymphatic channels is a possible CSF outflow pathway (10).

To find evidence of a CSF draining pathway within the meninges of the intraorbital part of the human optic nerve, we studied the ultrastructure of the dura of the human ON before and after injecting india ink into the SAS of the ON.

MATERIALS AND METHODS

This postmortem study was carried out in seven subjects without ocular disease. The subjects were obtained no later than 6 hours after death, following qualified consent for autopsies.

Specimen Preparation and Labelling

On removal of the orbital roof, the ocular globes, together with the optic nerves and the chiasm, were carefully dissected in situ from surrounding tissues. The optic nerves were ligated with a 6.0 silk suture proximal to the optic chiasm. Subsequently, the fixative (either neutral buffered 4% formalin or 2.5% glutaraldehyde) was injected slowly into the SAS with a 19-gauge needle. Special care was taken to avoid high-injection pressure, to minimize the risk of creating artefacts.

In two cases, to label the lymphatic vessels within the dura, india ink dissolved in 8% formalin (vol/vol = 1:1) was injected slowly under low pressure into the SAS at the level of the midorbital segment of the ON. The intact specimens were fixed in 4% formalin by immersion for 1 to 7 days before further dissection.

Light Microscopy

From each eye, a single piece including the midorbital and bulbar segment of the ON (Fig. 3A) was processed for paraffin blocks and cut in sections 5–8 μm thick. The
stains included haematoxylin and eosin, van Gieson elastic, and Masson trichrome.

**Scanning Electron Microscopy (SEM)**

For injection and immersion fixation, 2.5% glutaraldehyde solved in 0.05 mol/L cacodylate buffer was used. Transverse sections of the midorbital and bulbar segments were dehydrated in an acetone series, dried by the critical point method (CO₂), mounted on aluminium stubs, and sputtered with gold (approximately 30 nm). The specimens were analyzed with an SEM 505 (Philips, Eindhoven, the Netherlands) at an accelerated voltage of 20 kV.

**Transmission Electron Microscopy (TEM)**

After injection of 2% glutaraldehyde (0.1 mol/L cacodylate buffer) into the SAS, the globe and optic nerve were further fixed for at least 1 week by immersion in the same solution. Subsequently, small fragments (approximately 1 mm³) were cut from the optic nerve (midorbital and bulbar segments) and postfixed for 1 to 2 days in 1% OsO₄ (0.1 mol/L sodium phosphate buffer). The specimens then were dehydrated in an alcohol series and embedded into epon. Semithin sections were cut from each block (approximately 1 μm) and stained with toluidine blue to identify the meninges. Ultrathin sections (approximately 50 nm) were contrasted with uranyl acetate and lead citrate and studied with a CM 100 transmission electron microscope (Philips, Eindhoven, the Netherlands).

**RESULTS**

**Scanning Electron Microscopy**

In cross sections of the optic nerve, the arachnoid was found partially detached from the dura, forming an artificial subdural space (Figs. 1A and 1B). This artefact was caused by shrinkage of the specimen during SEM preparation. However, in each cross section, areas were found with the arachnoid lining in close contact to the dura, thus allowing detailed analysis of normal morphology of the SAS.

Distinct differences in the SEM appearance of the SAS were detectable between the midorbital and bulbar segments of the optic nerve (Fig. 1). In the midorbital segment, the SAS was bridged by coarse arachnoidal pillars that occasionally showed blood vessels running from dura to pia, and vice versa (Fig. 1A). In the bulbar segment of the ON, the SAS was significantly widened (Fig. 1B). The SAS contained a delicate network of branched trabeculae connecting the dural and pial surface of the arachnoid lining.

At higher magnification, the surface of the arachnoid cells appeared smooth, with no microvilli or other cell processes. However, small oval clefts (0.1 to 0.3 μm) were found in the dural level of the arachnoid layer (Fig. 1C). The number of lymphatic capillaries varied distinctly between the optic nerve segments. Lymphatic capillaries rarely occurred in the SAS of the midorbital part but were often detectable in the bulbar segment of the ON.

**FIG. 1.** Scanning electron microscopy appearance of optic nerve and adjacent meninges (cross sections). A: Midorbital segment with a few arachnoid pillars spanning between the dura and the pia of the narrow subarachnoid space; original magnification ×12. B: Bulbar segment displaying wide subarachnoid space with delicate network of trabeculae; original magnification ×12. C: High magnification of arachnoid surface lining the dura, displaying multiple pores; original magnification ×500.
Transmission Electron Microscopy

The dura was examined carefully by TEM to establish the morphology of the various vessel types. Blood capillaries with continuous endothelium supported by a well-defined basal lamina, as well as arteries, small arteries, and veins were detectable, although not very frequently. In addition, lymphatic capillaries were found and could easily be distinguished from blood capillaries by their typical ultrastructure (Fig. 2). The lymphatic capillaries were usually contiguous with collagen fiber bundles and embedded into an amorphous, moderately electron-dense extracellular matrix. The lymphatic capillaries were lined by extremely flat endothelial cells that lacked a basal lamina. The oval, heterochromatin-rich nucleus of the endothelial cells was surrounded by a thin layer of cytoplasm with few organelles. Occasionally, small aggregates of lipid droplets and lipofuscin granules were found along the endothelial lining; original magnification A x5500, B x6000.

Transmission Electron Microscopy

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FIG. 3. Labelling experiment, light microscopy. A: Gross morphology of india ink injected specimen. Note the concentric widening of the bulbar segment of the optic nerve. The lines indicate the levels where specimens were taken for light and electron microscopy. B: Midorbital segment of the optic nerve: india ink is clearly visible at the surface of the arachnoidal layer (arrows) and within slit-like vessels of the dura (arrow head); original magnification x20. C: Bulbar portion of the optic nerve displaying dense network of labelled vessels within the dura. Asterisk indicates the lumen of the subarachnoid space; original magnification x40.
ules were found in the perinuclear cytoplasm. The endothelial lining of the lymphatic capillaries was interrupted by small interendothelial pores, often found where the extracellular matrix was in direct contact with the electron-translucent lumen of the vessel (Fig. 2B).

Labelling Experiments

India ink was injected into the SAS to reveal a possible CSF drainage function of the lymphatic capillaries found in the dura. Gross inspection of the injected specimens clearly showed the dye as black deposits in the SAS beneath the dura (Fig. 3A). The ink deposits localized anteriorly at the level of the lamina cribrosa and the sclera remained unstained. Furthermore, differences in the extension of SAS between the midorbital and the bulbar part of the optic nerve became distinctly more pronounced. The bulbar segment regularly showed a spherical widening and a blind end at the level of the lamina cribrosa, reflecting a cul de sac shape.

With light microscopy, the india ink appeared as a black-stained deposit within the SAS and at the surface of the arachnoid layer (Figs. 3B and C). Labelling was further detectable within slit-like lymphatic channels of the adjacent dura. The stained lymph channels mainly were found in the inner third of the dura. Prevalence and distribution of lymphatics varied distinctly between the...

H.E. KILLER ET AL.

orlral segments studied. In the midorbital segment, a few unbranched lymph channels were usually detectable (Fig. 3B), whereas the dura of the bulbar segment displayed a complex network of labelled lymphatic vessels (Fig. 3C).

To follow possible lymphatic drainage routes of india ink, we studied the injected specimens with TEM (Fig. 4). The india ink was easily detectable as electron-dense granules of approximately 30 nm in diameter. Careful examination of the arachnoid layer revealed circumscribed areas where ink particles could be found spreading through intercellular clefts between the arachnoid cells (Fig. 4A). In addition, ink particles were detectable in the extracellular space of the dura, in close vicinity to endothelial cells of the lymphatic capillaries (Fig. 4B). Labelling was also found in the interendothelial pores and in the lumens of the lymphatic capillaries (Fig. 4B).

**DISCUSSION**

The ON represents an integral white-matter tract of the CNS. The ON can be divided into the intraorbital, the canaliculare, and the intracraniotal portions. The bulbal segment, or ampulla, is part of the intraorbital portion and is attached to the sciera of the ocular globe. The ON is surrounded by a meningeal envelope. The SAS of the ON communicates distal of the intracraniotal portion, with the chiasmal cystem and ends blind in the bulbal portion at the level of the lamina cribrosa, resembling a cul de sac. Cerebrospinal fluid inflow into the orbital portion of the SAS of the ON is supplied from the chiasmal cystem, and a reverse flux is to be expected, provided that CSF escape by alternative routes is insignificant. There is general agreement that the choroid plexus epithelium and the ependymal cells of the ventricular system are the principal sources of CSF production (15, 16, 26). An important site of CSF drainage into the major dural sinuses is in the arachnoid villius, which can be found in the optic nerve of humans and monkeys (15, 23). Other sites of absorption, including the choroid plexus (23, 24), the capillaries, the intercellular space of the brain (5), and the lymphatic channels have been discussed in scientific literature (10, 11, 17). The idea of a direct CSF penetration from the SAS through the arachnoid membrane and into the dura has found little acclaim in the past. In 1869, Schwabbe was the first author to demonstrate communication of the cranial SAS with the cervical lymphatic system. He introduced Prussian blue “under constant unspecific pressure” into the cranial SAS of rabbits, thereby claiming that lymphatic channels were the major drainage pathway for CSF (10). Schwabbe, however, did not perform histologic studies to provide morphologic proof for his hypothesis.

In a 1989 study, Mc Getrick et al. (37) failed to provide evidence for lymphatic vessels posterior to the conjunctiva in a monkey model. Exit of macromolecules from the subarachnoidal space at the termination of the optic nerve via “open channels” was described by Erlich (38). Brinker (40) provided evidence for CSF outflow along the optic nerve in rats, cats, dogs, and monkeys, after dye injection into the cisterna magna. Using enzyme histologic, light microscopic, and electron microscopic studies, Sherman et al. (39) demonstrated lymphatic vessels in the conjunctiva, the extraocular muscles, the lacrimal gland, and the arachnoid trabeculae. In 1994, Zenker et al. (9, 11) published the concept of diffuse absorption of CSF through the spinal meninges in the rat; cationized ferritin injections into the SAS of rat dorsal roots that showed active transport of this tracer into the surrounding dura were used. The morphologic counterpart for this observation was the presence of lymphatic clefts in the dura matter of the meningeal funnels in the rat (9). Földi demonstrated lymphatic vessels in the lacrimal system, the conjunctiva, and the cornea (4), as well as in the skull base (13, 18, 19). He suggested that lymph drainage occurred from orbital structures into the nodal system of the neck. Experimental support for his concept of CNS lymphatics resulted from his observation of relief of papilledema upon blockage of the stellate ganglion in dogs. The dogs previously were subjected to ligation of lymph vessels and of their expected tributary lymph nodes in the neck (2, 3, 6, 7, 12). Briefly (14) introduced ink into the cranial SAS that appeared in mid thoracic and cervical lymph nodes as well as in the lumbar and sacral nerve roots. Although CSF drainage into lymphatics has been shown to exist in the CNS (34, 35, 36, 40), it was never shown to exist in the human optic nerve; the existence of a lymphatic system in the optic nerve was strongly opposed by Hayreh (20), who denied the existence of lymphatic vessels in the entire central nervous system.

To investigate the structures possibly involved in CSF drainage in the meninges of the intraorbital portion of the human ON, we performed the present morphologic study. We were able to demonstrate that ink enters into lymphatic capillaries in the dura of the human ON upon injection of the SAS, possibly via slit-like pores in the neurothelial layer of the arachnoid membrane, indicating a functional drainage system for CSF from the SAS of the ON into the dura. Because the blind end of the SAS in the bulbar segment of the ON resembles a cul de sac at the level of the lamina cribrosa, CSF turnover is expected to be very slow in that narrow compartment, especially if there is no drainage system in this minute compartment. Our discovery of intradural lymphatic capillaries, which are predominantly located in the bulbar part of the ON, and the results of our tracer studies indicate CSF drainage from the SAS of the bulbar part of the ON into the meninges of the ON.

Little is known about the CSF pressure in the SAS of the optic nerve. Until now, the concept of a homogeneous pressure in the entire CSF compartment, including ventricles, SAS, and cysterns, has not been seriously challenged. Direct measurements of CSF pressure in the SAS of the ON are technically difficult to perform and tend to be unreliable because of the small size and trabeculation of this compartment (25). Indirect methods, such as ultrasound studies of the diameter of the ON.
under increasing volume pressure, may be a promising approach in the future (26,27). Individual sheath elasticity and individual degree of trabeculation and septae between the arachnoid and pia in the SAS, however, may limit the value of such studies.

To prevent accumulating CSF pressure in the bulbar part of the ON, which may cause papilledema and probably pressure-related malperfusion of the feeding pial arteriolar system of the ON (22), a functional CSF outflow system appears to be desirable. In addition to arachnoid villi in the meninges of the ON (33), our morphologic findings provide another anatomic basis for such a drainage system. Intradural lymphatic vessels further may help to understand phenomena such as unilateral papilledema (28,29), pseudotumor cerebri without papilledema (30), pseudotumor cerebri with normal intracranial pressure (31), or the pathophysiology of the retrograde part of axonal degeneration in normal tension glaucoma (private communication with J. Flammer, Department of Ophthalmology, University of Basel). This study may give further histologic evidence for the route of CSF outflow from the SAS of the optic nerve that has been described in the literature (38,41). Additional studies are necessary to define the physiologic purpose of lymphatic capillaries in the meninges of the human optic nerve.

Acknowledgements

The authors thank P. Gerber (Institute of Pathology, Kantonsspital Aarau, Switzerland) for careful preparation of the optic nerves used in this study, as well as P. Rosenbaum, M.D., (Albert Einstein College of Medicine, Bronx, New York, NY), who prepared some of the nerves used in this study for electron microscopy studies.

We also thank R. M. Burde (Albert Einstein College of Medicine, New York, NY) for continuous inspiration, as well as for reading this manuscript.

Special thanks to Professor W. Zenker, who inspired us with his previous publications.

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Opsoclonus in a Patient With Cerebellar Dysfunction

Maurizio Versino, M.D., Andrea Mascolo, M.D., Giovanni Piccolo, M.D., Roberto Alloni, and Vittorio Cosi, M.D.

After two days of malaise, headache, nausea, and vomiting, a 26-year-old man suddenly developed opsoclonus and stance and gait ataxia, without myoclonus. Having excluded a paraneoplastic etiology, we assumed that the disorder was probably related to a viral infection. Spontaneous resolution occurred in about two months. Opsoclonus became flutter dysmetria and then resolved. Saccadic eye movement recording disclosed the occurrence of hypermetria, increased velocity, and delayed latency, which also resolved. In this patient, the correspondence between clinical and ocular motor abnormality courses suggests a transient cerebellar dysfunction as the possible pathophysiology mechanism for opsoclonus.

Key Words: Cerebellum—Opsoclonus.

Opsoclonus consists of involuntary conjugate saccadic oscillations in all directions, without intersaccadic interval. Onset can be gradual or abrupt, and oscillations can be as large as 30-40° (mean: 10-20°); they may be continuous, or may present as series of 2-13-Hz bursts lasting 5-7 seconds (1). They may persist in sleep, and may be associated with other symptoms and signs, including myoclonus, cerebellar signs, and decreased mental status (2). About 50% of cases are idiopathic, and probably include some undiagnosed viral encephalitis. About 20% of cases are paraneoplastic (3), and other causes include infectious, metabolic, and toxic diseases (2). The pathophysiology of opsoclonus, however, is still unclear (4).

We describe a patient who developed an opsoclonus; the course of clinical and ocular motor signs suggested a cerebellar impairment.

CASE REPORT

A 26-year-old man suddenly complained of "shaking vision" and of stance and gait difficulties after two days of malaise, severe headache, nausea, and vomiting. Initially, he was admitted to a local hospital with a diagnosis of possible meningococcemia. Shortly after admission, he developed a psychomotor agitation that remitted with neuroleptic and benzodiazepine administration. He was treated with ceftriaxone and acyclovir without significant improvement of neurologic symptoms.

On admission to our center, about 10 days after symptom onset, he had a mild degree of agitation but he was alert and well oriented. Neurologic examination revealed: opsoclonus, which was mainly horizontal not enhanced by fixation and reduced in lateral gaze; generalized hypotonia; truncal ataxia and an inability to walk or to stand without human support. There was no myoclonus. Routine laboratory studies disclosed normal values, with the exception of creatine phosphokinase level (4,150 U/L) with normal motor strength, probably related to the psychomotor agitation mentioned above, which normalized before discharge. The serum antibody levels for herpes simplex virus, cytomegalovirus, Epstein Barr virus, hepatitis B virus, and human immunodeficiency virus were normal. The level of urinary catecholamines was normal. Cerebrospinal fluid examination only showed a mild lymphocytic pleocytosis (25 cells/mm³) with normal albumin and IgG content, normal IgG index, and polyclonal distribution of both CSF and serum IgG. Neither serum nor CSF showed any immunohistochemical reactivity against rat cerebellar tissue. Results of computed tomography and MRI of the head, chest radiograph, and thyroid and testicle echography were normal. Electroencephalography showed bilateral frontal beta activity, sporadic bilateral anterior theta waves, and periods of drowsiness.

The patient was treated with steroids (6-methylprednisolone 250 mg i.v., for 10 days) and with clonazepam (4 mg/day), and slowly improved.

Before discharge, about 40 days from symptom onset, he still showed mild truncal, stance, and gait ataxia; opsoclonus had become flutter dysmetria (Fig. 1), i.e., a transient burst of horizontal back-to-back saccades at the end of each voluntary or reflexive saccade. One month later, he was symptom free, and neurological examination showed nothing abnormal, with the exception of some saccadic oscillations still present at the end of saccades, which disappeared only 4 months later. After 1 year, the only remaining detectable signs were some saccadic oscillations at the end of divergence eye movements.

We were able to study reflexive saccades only shortly before discharge and at the subsequent outpatient check-
FIG. 1. The left (continuous line) and right (dotted line) eye tracings of a 10° leftward saccade recorded monocularly with the infrared reflection technique (Skalar IROG system) at 40 (A), 100 (B), 220 (C), and 580 (D) days from symptom onset. Saccades proved to be hypermetric, and ended with flutter dysmetria in (A); this pattern was clearly attenuated in (B), and disappeared in both (C) and (D).

ups. Figure 1 shows the evolution of flutter dysmetria, and Table 1 reports the saccade parameters. Saccade parameters were obtained by binocular electrooculographic recordings with a reflexive saccade paradigm (see ref. 10 for more details). In each recording session, the patient made about 56 saccades from primary position and target displacement ranged from 5 to 35°. In the first recording session, made shortly before discharge, we were able to collect only 20 saccades, mainly for 5 and 10° target displacements. When measured shortly before his discharge, saccades were mainly hypermetric in all directions, and showed a delayed latency, whereas peak velocity and duration were "supernormal." After 2 months, saccades were only slightly hypermetric, and were normal 4 months and 1 year later.

**DISCUSSION**

Our patient presented an opsoclonus associated with other neurologic signs that were probably viral in origin, which spontaneously resolved themselves.

It is not yet established whether the cerebellum or the brainstem, or both, are involved in the pathophysiology of opsoclonus (4). In our patient, the disappearance of flutter dysmetria, which followed opsoclonus, matched the saccade shift from hyper- to normometria. This suggests a reversible dysfunction involving the cerebellar fastigial nuclei (FN), which tailor saccade accuracy and control saccade acceleration and deceleration through connections to brainstem ocular motor structures (5). The latter include the inhibitory projections from caudal FN to omnipause neurons, which in turn tonically inhibit the saccade burst generator to prevent saccadic intrusions (6), and gate the burst generator activity during saccades. Accordingly, a miscontrol on omnipause neurons by FN may explain saccade oscillations (7), saccade dysmetria, (8) and, possibly, the increased saccade velocity detectable at the first saccade recording session (9). The latter finding implies a cerebellar involvement in saccade dynamic, but it must be considered cautiously because, at the first recording session, the patient was still bothered by the oscillopsia he complained of at the end of each saccade, and we were able to collect 20 saccades, most of which for small target displacement. However, a recent article showed that saccade velocity was reduced by a lesion affecting the oculomotor vermis but not the FN.

**TABLE 1. Saccade parameters at different times from symptom onset**

<table>
<thead>
<tr>
<th>Time from onset (days)</th>
<th>Duration (mos)</th>
<th>Peak velocity (degrees)</th>
<th>Gain</th>
<th>Latency (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 (discharge)</td>
<td>61.05</td>
<td>1,010</td>
<td>2.68</td>
<td>322.7</td>
</tr>
<tr>
<td>100</td>
<td>83.11</td>
<td>584</td>
<td>1.03</td>
<td>298.5</td>
</tr>
<tr>
<td>220</td>
<td>93.96</td>
<td>450</td>
<td>0.88</td>
<td>230.8</td>
</tr>
<tr>
<td>580</td>
<td>91.72</td>
<td>469</td>
<td>0.89</td>
<td>221.9</td>
</tr>
<tr>
<td>Normal range (95% confidence interval)</td>
<td>63.4-93.1</td>
<td>397-915</td>
<td>0.87-1.03</td>
<td>176-321</td>
</tr>
</tbody>
</table>

Duration is the theoretical saccade duration for 20° saccade amplitude derived from the amplitude-duration relationship computed from the patient's duration and amplitude raw data by means of linear regression. Peak velocity corresponds to the maximum (saturation) peak velocity value, for a theoretical saccade of infinite amplitude, derived from the amplitude-peak velocity relationship computed from the patient's peak velocity and amplitude raw data by means of linear regression. Gain is the mean value of the ratios of real to desired saccade amplitude (i.e., target displacement). Latency is the mean value of the delays from target displacement and saccade onset.
This datum is in keeping with our finding because the oculomotor vermis outflow consists of inhibitory projections to the FN; accordingly, a lesion involving the FN should increase saccade velocity. In our patient, the occurrence of hypermetric saccades suggests a FN impairment (8). Moreover, FN impairment may explain the truncal, stance, and gait ataxia, because the rostral FN projects to the vestibular nuclei. Finally, the initial saccade latency delay and the subsequent latency reduction can be explained by the titration of clonazepam.

We conclude that this case of opsoclonus, which was not associated with a cancer and recovered, can be considered a cerebellar dysfunction on the basis of the evolution of other concomitant ocular motor and clinical signs.

REFERENCES
Toxic Optic Neuropathy After Concomitant Use of Melatonin, Zoloft, and a High-Protein Diet

Norman L. Lehman, M.D., Ph.D., and Lenworth N. Johnson, M.D.

Melatonin is a hormone produced by the pineal gland and retina, and is involved in light-dark circadian rhythms (1). It is used as a holistic sleep aid and touted cure for several ailments (2). Some researchers have cautioned against possible side effects of melatonin supplementation including cerebral and coronary vasoconstriction, infertility, and retinal damage (2). Zoloft (sertraline; Pfizer Inc., New York, NY) is a commonly used antidepressant drug belonging to the selective serotonin reuptake inhibitor (SSRI) category. We report a case of possible toxic optic neuropathy associated with concomitant use of Zoloft and supplemental melatonin.

**CASE REPORT**

A 42-year-old woman developed blurred vision, reduced color vision, decreased brightness sensation when indoors, and outdoor photosensitivity 2 weeks after initiating a high-protein diet with melatonin supplementation (1 mg daily). Additionally, she reported imbalance and restless sleep. She previously enjoyed excellent health apart from depression, for which she had taken Zoloft 100 mg daily for 4 years. Her best corrected visual acuity was 20/50 OD and 20/60 OS. Automated perimetry (Humphrey 120-point screen) initially was normal for the left eye, but showed a central scotoma for the right eye. Twelve days after discontinuing melatonin and resuming a normal diet, her visual acuity improved to 20/30 in each eye (OU). She correctly identified only 1 and 5 of 17 Ishihara color plates with the right and left eyes, respectively. Humphrey automated perimetry (program 24-2) showed a cecocentral scotoma OD and central scotoma OS (Fig. 1A). The remainder of the neuro-ophthalmologic examination including pupillary examination, slit-lamp biomicroscopy, and fundoscopic examination were normal. A magnetic resonance imaging scan of the cranium and orbits was normal.

One month later, her visual acuity was 20/30 OD and 20/25 OS. Automated perimetry showed cecocentral scotoma OU (Fig. 1B). Color vision was unchanged. The neurologic examination was normal. Two months after stopping melatonin and the high-protein diet her visual acuity was 20/25 OU. Her color vision improved to correctly identifying 12 of 17 color plates with the right eye and all 17 color plates with the left eye. Automated perimetry performed 6 months after the initial visit showed normal results (Fig. 1C).

**DISCUSSION**

Bilateral visual acuity loss, cecocentral scotomas, and dyschromatopsia suggest toxic, hereditary, demyelinating, compressive, or infiltrating optic neuropathy. Although mitochondrial DNA analysis was not performed, the absence of optic disc telangiectasia, lack of family history, and rapid recovery of vision renders Leber's hereditary optic neuropathy unlikely. Absence of retrobulbar pain, normal neuroimaging, and rapid resolution of signs and symptoms after discontinuation of melatonin and the high-protein diet are most consistent with toxic optic neuropathy.
Melatonin and the neurotransmitter-neuromodulator dopamine both undergo diurnal release in the retina. Retinal melatonin levels peak under dark conditions, whereas dopamine peaks during light (1). Dopamine is important in visual acuity, color vision, and contrast sensitivity (3-5). Dopamine, which is produced by retinal amacrine and interplexiform cells, affects photoreceptors and horizontal cells, and reduces spontaneous firing rates and light-evoked responses of ganglion cells (6). Melatonin is involved in light–dark adaptation. Melatonin inhibits both dopamine release and dopamine function at D₁ receptors (3). The melatonin antagonist luzindole in-

**FIG. 1.** Humphrey automated perimetry (program 24-2) shows left central scotoma and right cecocentral scotoma at 1 month (A), bilateral cecocentral scotomas at 2 months (B), and resolution of scotomas at 6 months (C) after discontinuation of melatonin supplementation and the high-protein diet.
hibits melatonin's ability to decrease dopamine release and protects dark-adapted rat photoreceptor cells from light damage (7). Dopamine action at D2-receptor sites results in reduced melatonin via inhibition of the expression of the key regulatory enzyme in the conversion of serotonin to melatonin, serotonin N-acetyltransferase (1). Thus, dopamine and melatonin mediate retinal processes in a reciprocal manner.

SSRIs increase levels of serotonin at the neural synapse. Exogenous administration of the amino acid precursors of serotonin, namely, tryptophan and 5-hydroxytryptophan, increase central nervous system serotonin levels (8) and retinal melatonin levels (9), respectively. A diet depleted in tryptophan decreases brain serotonin. Depending on its composition, a high-protein diet may also decrease brain serotonin because of preferential absorption of competitive neutral amino acids in the brain (10), although to our knowledge, a similar effect in the retina has not been described. Inhibition of serotonin axonal reuptake by a SSRI may result in an increased supply of serotonin as a melatonin precursor for neighboring cells.

We suspect that our patient had relatively high retinal melatonin levels because of the combined effects of Zoloft, the high-protein diet, and exogenous melatonin supplementation, resulting in decreased dopamine-mediated retinal activity with resultant indirect and direct effects on ganglion cells. Because an electroretinogram, pattern and standard visual evoked potentials were not performed, it remains uncertain whether the initial dysfunction was caused by a nonspecific retinal disorder or specific retinal ganglion cell damage (optic neuropathy). The patient could have been rechallenged with melatonin to confirm the toxic reaction; however, the risk of incomplete recovery renders such testing unethical.

In summary, the combined use of melatonin and Zoloft, and possibly a high-protein diet, may be associated with retinal melatonin/dopamine imbalance manifesting as possible toxic optic neuropathy. Physicians and patients should be alerted to this potential drug interaction.

Acknowledgment: Supported in part by an unrestricted grant from Research to Prevent Blindness, Inc. (New York, New York) to the Mason Eye Institute, University of Missouri-Columbia.

REFERENCES


Optic Nerve Enhancement on Magnetic Resonance Imaging in Arteritic Ischemic Optic Neuropathy


Although optic nerve enhancement may be seen in magnetic resonance imaging of radiation-induced ischemic optic neuropathy, similar enhancement in ischemic optic neuropathy has not been previously reported in the English-language neuro-ophthalmologic literature. We report three cases of optic nerve enhancement in biopsy-proven arteritic ischemic optic neuropathy. Clinicians should consider giant cell arteritis in the differential diagnosis of an optic neuropathy with optic nerve enhancement on magnetic resonance imaging.

Key Words: Ischemic optic neuropathy—Optic nerve enhancement.

Optic nerve enhancement after the administration of gadolinium contrast material on magnetic resonance imaging is a nonspecific but pathologic finding. Although such enhancement of the optic nerve has been reported previously in neoplastic, inflammatory, radiation-induced, infiltrative, and infectious optic neuropathies, to our knowledge this finding has not been described in non-radiation-induced ischemic optic neuropathy (1). We describe three cases of optic nerve enhancement in ischemic optic neuropathy (ION) caused by biopsy proven giant-cell arteritis (GCA).

CASE REPORTS

Case 1

An 82-year-old woman developed acute, bilateral visual loss on awakening on June 1, 1994. She had had a 2-month history of anorexia, scalp tenderness, and jaw claudication. Past medical history was significant for coronary artery disease, myocardial infarction, and diabetes mellitus. Neuro-ophthalmic examination on June 8, 1994 revealed a visual acuity of 20/400 in the right eye (OD) and no light perception in the left eye (OS). Goldmann kinetic perimetry revealed a residual superotemporal island to the V4c stimulus OD. Ophthalmoscopy revealed bilateral pallid optic disc edema. Westergren erythrocyte sedimentation rate (ESR) was elevated at 113 mm/h. Magnetic resonance (MR) scan of the head revealed bilateral optic nerve enhancement after the administration of gadolinium-DTPA (Fig. 1). A temporal artery biopsy demonstrated findings consistent with GCA. The patient was treated with intravenous methylprednisolone (1,000 mg/d) followed by oral prednisone tapered slowly. Visual function remained unchanged.

Case 2

An 86-year-old woman developed acute, bilateral visual loss on July 24, 1994. Past medical history was significant for diabetes mellitus, coronary artery disease,
hypothyroidism, and ischemic cardiomyopathy. She had a 6-week history of fatigue, scalp tenderness, anorexia, and jaw claudication. Neuro-ophthalmologic examination on August 2, 1994 revealed a visual acuity of counting fingers at 1 m OD and no light perception OS. Goldmann kinetic perimetry revealed a small temporal island to the V4e stimulus OD. Ophthalmoscopy revealed diffuse optic nerve pallor OD and pallid optic disc edema with peripapillary hemorrhage OS. MR scan of the orbit with fat suppression revealed bilateral enhancement of the optic nerves after gadolinium-DTPA. Westergren ESR was 85 mm/h. A temporal artery biopsy was positive for GCA. The patient was treated with oral steroids and the visual function stabilized.

Case 3
An 80-year-old man developed new-onset headaches, scalp tenderness, weight loss, and fatigue during a 3-month period. In January 1999, he developed loss of vision OS and was diagnosed with a nonembolic branch retinal artery occlusion. ESR was 20 mm/h. A carotid Doppler study showed normal results. In April 1999, 3 months after the visual loss OS, he developed acute painless loss of vision OD. Examination revealed a visual acuity of counting fingers OD and 20/20 OS. There was a right relative afferent pupillary defect. Ophthalmoscopy of the OD revealed a normal retina and optic nerve. There was mild superior retinal artery narrowing OS and mild optic atrophy OS. ESR was 95 mm/hr. MR scan of the head and orbit revealed mild bilateral optic nerve enhancement after gadolinium-DTPA (Fig. 2). The patient was treated with intravenous methylprednisolone 1,000 mg/d for 3 days followed by an oral prednisone taper. A right temporal artery biopsy was positive for active GCA.

DISCUSSION
Ischemic optic neuropathy (ION) is the most common acute optic neuropathy of older adults. The anterior form of ION (AION) is characterized by optic disc edema, whereas the posterior or retrobulbar form shows no optic disc edema (PION). AION may be caused by GCA (arteritic AION) or more commonly, may occur without arteritis (nonarteritic AION, or NA-AION). Although MR imaging of the head is usually not required in typical AION, imaging should be considered in atypical cases. Atypical features might include bilateral and simultaneous onset optic neuropathy (case 1), optic atrophy and contralateral optic disc edema (pseudo-Foster-Kennedy syndrome) (case 2), or retrobulbar (PION) optic neuropathy (case 3). In all three of our cases, MR imaging was performed to exclude other etiologies of a bilateral acute optic neuropathy (e.g., infiltrative inflammatory, neoplastic etiologies).

In all of our cases, MR scan revealed optic nerve enhancement after the administration of gadolinium-DTPA. However, enhancement of the optic nerve on MR scan is not specific. This finding may occur in any process that disrupts the blood–brain barrier, including the following: 1) infiltrative or inflammatory (e.g., sarcoid, Wegener granulomatosis); 2) demyelinating (optic neuritis); 3) infectious (e.g., syphilis); and 4) neoplastic (e.g., optic nerve meningiomas, gliomas, metastatic lesions, carcinomatos meningitis) optic neuropathies (1). Typically, enlargement as well as enhancement occurs in patients with optic nerve tumors. There was no evidence of optic nerve enlargement or optic nerve tumor in any of our cases.

Although ischemia caused by radiation necrosis of the optic nerve may show enhancement on MR, we are unaware of any reports in the English-language literature of ION and enhancement of the optic nerve. An MR scan is not generally indicated in typical NA-AION, but a few papers have reported the MR findings in this condition. Arnold et al. (2) described MR imaging of the brain in 13 patients with NA-AION and reported an increased number of central nervous system white matter lesions. Although not the primary goal of their article, optic nerve enhancement was not seen in these patients (personal communication, Anthony Arnold, M.D.). Jay and Williamson performed MR scans on nine patients with NA-AION and reported only white matter ischemic lesions, and no comment was made on optic nerve enhancement (3). Jay and Williamson believed that AION might involve microvascular changes that are undetectable with an MR scan (3). Although we do not recommend MR imaging for NA-AION, many patients are referred for neuro-ophthalmic evaluation after having already completed an MR scan. We have never encountered a case of optic nerve enhancement in NA-AION. Unfortunately, our work does not answer the question regarding optic nerve enhancement on MR scan.
in NA-AION. To our knowledge, this is the first report of MR imaging enhancement of the optic nerve in arteritic ION. We suspect that the pathophysiology of arteritic ION in our cases is different from NA-AION. The presumed pathophysiology of NA-AION is microvascular ischemia of small posterior ciliary vessels of the anterior optic nerve. The ischemia in arteritic ION in either the anterior or posterior form is presumably caused by a more widespread inflammatory vasculitis involving the posterior optic nerve and choroidal circulation and thus may be more likely to demonstrate enhancement because of blood–brain barrier disruption. Clinicians should be aware that arteritic ION might cause optic nerve enhancement on MR and that NA-AION is less likely in this setting.

Acknowledgment: This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY and the Baylor Neuro-ophthalmology Academic Fund.

REFERENCES

Optic Nerve Enhancement on Orbital Magnetic Resonance Imaging in Leber’s Hereditary Optic Neuropathy

Michael S. Vaphiades, D.O., and Nancy J. Newman, M.D.

An 18-year-old man with Leber’s hereditary optic neuropathy and bilateral visual loss had optic nerve enhancement on T1-weighted orbital fat-suppressed magnetic resonance imaging. To our knowledge, this is the first reported case of optic nerve enhancement on orbital magnetic resonance imaging in Leber’s hereditary optic neuropathy.

Key Words: Enhancement—Leber’s hereditary optic neuropathy—Optic nerve.

CASE REPORT

In the first week of November 1996, an 18-year-old man noted painless sequential visual loss in the right eye (OD), followed by these same symptoms in the left eye (OS) 2 weeks later. He had no contributory medical history. The neuro-ophthalmologic examination revealed a visual acuity of count fingers vision OD and 20/80 OS. Color vision was 0/14 OD and 7.5/14 OS using the Ishihara pseudo-isochromatic plates. Goldmann perimetry showed large central scotomas in both eyes (OU). Pupils were 7 mm OU with normal reactivity, and there was a 0.9 log unit right relative afferent pupillary defect. Motility and slit-lamp examination results were normal. Ophthalmoscopy showed disc elevation with obscuration of the disc margins OU. A detailed neurologic examination yielded otherwise normal results.

Magnetic resonance imaging (MRI) of the brain and orbits with and without orbital fat suppression and gadolinium administration on December 16, 1996, demonstrated enhancement of the optic nerves bilaterally (Fig. 1). Chest radiography findings, complete blood count, syphilis serology, angiotensin converting enzyme, Bartonella henselae titer, Lyme titer, HIV test results, and lumbar puncture results were normal. Mitochondrial DNA testing revealed a mutation at nucleotide position 3460 which is, compatible with the diagnosis of Leber’s hereditary optic neuropathy (LHON).

DISCUSSION

Leber’s hereditary optic neuropathy is a maternally inherited neuropathy associated with point mutations in the mitochondrial DNA. The orbital MRI findings are typically normal, although an increased signal from the retrobulbar optic nerve has been reported on T2-weighted fast spin echo (1) and short time inversion recovery sequences (2). Mashima et al. reported four patients with LHON for whom orbital T1-weighted MRI scans were performed with fat suppression and gadolinium within 4 weeks of visual loss. None of these patients had optic nerve enhancement after gadolinium administration, although increased signals from the retrobulbar optic nerves were noted on T2-weighted fat suppressed sequences (1). Previous MRI studies of the optic nerves in patients with LHON did not use orbital fat suppression with gadolinium, and therefore the presence or absence of optic nerve enhancement was not addressed (2-4). It is perhaps not surprising, given the pathology of affected optic nerves that the site of MRI abnormality within the optic nerves in patients with LHON is not limited to the prelaminar portion of the nerve. Indeed, optic nerve cross-sections of patients with LHON have shown fibrocystic scarring in the retrobulbar portion (5).

Gadolinium does not cross an intact blood-brain barrier, and enhancement with gadolinium administration denotes disruption of the blood-brain barrier within the optic nerve (6). The affected optic nerve enhances because gadolinium induces a local magnetic field, resulting in a bright signal on T1-weighted fat-suppressed images (6). Orbital fat suppression is usually necessary to visualize the optic nerve enhancement because of the large amount of bright fat in the orbits (6-8). Typical lesions that result in optic nerve enhancement include optic neuritis, radiation-induced optic neuropathy, and optic nerve tumors (6,9).

It is unclear why the patients with LHON reported by Mashima et al. did not exhibit optic nerve enhancement after gadolinium administration, especially given that all four patients were within the acute phase of visual loss.
Their patients all harbored the 11778 mitochondrial DNA mutation, whereas ours had the 3460 mutation, but that difference is unlikely to have influenced optic nerve pathology. Perhaps, as Mashima et al. suggested, the acute pathology in LHON is preliminary and intraocular, and it takes weeks to months for pathologic findings to involve the retrobulbar optic nerve (1). Our patient with LHON was imaged 6 weeks after first eye involvement and 4 weeks after second eye involvement.

To our knowledge, ours is the first reported case of a patient with LHON who has demonstrated enhancement of the optic nerves on fat-suppressed gadolinium-enhanced T1-weighted MRI of the orbits. The presence of optic nerve enhancement in a patient with optic neuropathy does not rule out the diagnosis of LHON.

Acknowledgment: This work was supported in part by an unrestricted grant from the Research to Prevent Blindness, Inc., New York City NY.

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FIG. 1. Coronal (left) and axial (right) fat-suppressed gadolinium-enhanced T1-weighted MRI of the orbits, showing optic nerve enhancement bilaterally.
Cat-Scratch Disease Presenting as Neuroretinitis and Peripheral Facial Palsy

P. Keith Thompson, B.S., Michael S. Vaphiades, D.o., and Michael Saccente, M.D

A 40-year-old woman with Cat-scratch disease sought treatment for neuroretinitis OD and right peripheral facial nerve palsy. To our knowledge, this is the first case of an adult with a peripheral facial nerve palsy from Cat-scratch disease and the first case of a patient with both neuroretinitis and peripheral facial nerve palsy.

Key Words: Bartonella henselae—Cat-scratch disease—Macular star—Neuroretinitis—Peripheral facial nerve palsy.

CASE REPORT

In September 1998, a 40-year-old woman developed a rash, a low-grade fever, chills, and neck tenderness following a kitten scratch. Five weeks later she developed painless visual loss OD. Neuro-ophthalmologic examination revealed a visual acuity of 20/30 OD and 20/15 OS, and use of Ishihara pseudo-isochromatic color plates revealed color vision of 13.5/14 OD and 11/14 OS. Goldmann perimetry showed a small central scotoma to the I2e isopter OD and a full visual field OS (Fig. 1). Pupils were 5 mm OU, with normal reactivity; there was no relative afferent pupillary defect. Motility and slit-lamp examinations were normal, showing no vitreous cells. Ophthalmoscopy revealed a mildly elevated optic nerve with a macular star OD (Fig. 2) and a normal optic nerve and macula OS. The patient had no skin lesions, cervical lymphadenopathy, parotid gland enlargement, or auricular lesions. A detailed neurologic examination was normal. The patient was prescribed oral double-strength trimethoprim-sulfamethoxazole (160 mg trimethoprim and 800 mg sulfamethoxazole) twice a day for 10 days for a presumed Bartonella henselae infection. Five days later she developed a mild right lower motor neuron facial palsy. The results of her examination were otherwise unchanged. Oral corticosteroids were offered, but the patient declined.

Testing included a complete blood count, determination of electrolytes and glucose levels, toxoplasmosis and a Lyme titer, and a Venereal Disease Research Laboratory (VDRL) test, the results of which were normal. B. henselae titer showed an IgG of 0.8 (<0.9) and an elevated

FIG. 1. Goldmann perimetry showing a central scotoma to the I2e isopter OD and a full visual field OS.
IgM of 2.1 (<1.1). Results of gadolinium-enhanced magnetic resonance imaging of the brain were normal.

Examination 1 month later showed a visual acuity of 20/15 OU. Ophthalmoscopy showed a resolving macular star OD. The right peripheral facial palsy had resolved.

DISCUSSION

Cat-scratch disease (CSD) is a systemic infection from the gram-negative bacilli *B. henselae*, which is transmitted by the bite or scratch of an asymptomatic feline carrier. Cat-scratch disease usually presents as a benign chronic lymphadenitis, although central nervous system involvement, including neuroretinitis and cranial neuropathies, has been reported (1–6). Cat-scratch disease has been associated with a facial nerve palsy in pediatric patients with ages ranging from 18 months to 9 years (5,7,8). The facial palsy is most likely caused by vasculitis of the nerve itself or by irritation of nervous structures and vasculature by an enlarged, inflamed parotid gland (2,6,8,9). Before this case report, only one patient was reported with a peripheral nerve palsy (median nerve palsy) and neuroretinitis (10).

To our knowledge, this is the first case of an adult patient with a peripheral facial nerve palsy from CSD, and the first patient with both a peripheral facial nerve palsy and neuroretinitis (1–12). For patients with neuroretinitis and a lower motor neuron facial palsy, it is important to consider CSD in the differential diagnosis.

Acknowledgment: This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY.

REFERENCES

Divergence Paresis: A Nonlocalizing Cause of Diplopia

Frederick E. Lepore, M.D.

Objectives: To determine the causes, clinical characteristics, and localizing value of divergence paresis, which is characterized by acquired and uncrossed diplopia when viewing distant targets, fusion when viewing near targets, and no limitation of ocular ductions. Controversy persists regarding the diseases underlying divergence paresis and the existence of a divergence "center."

Materials and Methods: The charts of 15 patients with divergence paresis examined between 1983 and 1998 were reviewed. All patients underwent neuroimaging and detailed ocular motility testing, with measurement of esotropia in prism diopters in 14 patients.

Results: Divergence paresis in 15 patients was idiopathic in three patients, was associated with central nervous system microangiopathy or infarct in seven patients, and chronic lymphocytic leukemia with sinusitis, Wernicke ophthalmoplegia, Parkinson disease, myasthenia gravis, cryptic cerebellar vascular malformation, and childhood esotropia in one patient each (two patients had two diagnoses). The mean maximum esotropia was 10.4 prism diopters, and there was no significant correlation (Fisher exact test) between the magnitude of esotropia and vasculopathic etiology or posterior fossa lesion site. Although six patients had posterior fossa disease, neuroimaging showed no common circumscribed lesion site or evidence of increased intracranial pressure.

Conclusions: Divergence paresis is an uncommon cause of acquired diplopia. Divergence paresis is associated with diverse central nervous system diseases and can be mimicked by myasthenia. The absence of a single consistent lesion in our study, which is the largest reported series, suggests that divergence paresis is a nonlocalizing cause of horizontal diplopia and that multiple or diffusely distributed neural structures may govern divergence. Alternatively, elusive divergence "centers" may not exist, and divergence paresis may arise from impaired inhibition or from defective passive antagonism of orbital structures to convergence.

Key Words: Abducens paresis—Diplopia—Divergence weakness.

Duane's (1) 1905 report of 11 patients with "very troublesome cases of esophoria" clearly delineated the clinical entities of divergence paralysis and paresis, which had initially been described by Parinaud (2) in 1883. Distinguishing features of this disorder of ocular motility included marked esophoria, insuperable or varying homonymous (uncrossed) diplopia for distance, normal or nearly normal relations for near, and no impairment of outward nor excess of inward rotations of the eyes (3). More than a century later, controversy persists regarding whether disorders of ocular divergence may aid in neuroanatomic localization. The important clinical questions surrounding the frequency of associated neurologic diseases, the implications of the varying severity of divergence weakness, and the relationship of divergence paresis to disorders of the abducens nerve remain, in addition to discerning the anatomic underpinnings of divergence paresis. This study of 15 patients with divergence paresis uses neuroimaging and detailed measurements of esotropia to reconcile existing definitions of divergence paresis with the phenomena actually encountered by clinicians, to document the frequency of associated neurologic diseases, and to speculate on the neural substrate for ocular divergence.

MATERIALS AND METHODS

I reviewed the charts of 15 patients with ocular esodeviation for distant targets, fusion for near targets, and full ocular ductions. The study included all patients with divergence paresis who were evaluated in the author's university-based, neuro-ophthalmology out-patient practice between 1983 and 1998. A complete neuro-ophthalmologic examination was performed on each patient, and prism diopter measurements of distance esotropia in different fields of gaze were obtained for 14 patients. All patients underwent neuroimaging (14 patients underwent magnetic resonance imaging, and one patient underwent computed tomography).

RESULTS

The mean age of the 15 patients (nine men and six women) was 58.6 (range, 14 to 80 years). All eyes tested had better than 20/30 visual acuity. Divergence paresis was isolated in three patients; was associated with central
DIVERGENCE PARESIS

nervous system (CNS) microangiopathy or infarct in
seven patients; and was associated with clivus lymphoma,
chronic lymphocytic leukemia with sinusitis, Wernicke ophthalmoplegia, Parkinson disease, myasthenia gravis, cryptic cerebellar vascular malformation, and childhood esotropia in one patient each (two patients had two diagnoses) (Table 1).

The mean maximum esotropia for distant target was 10.4 prism diopters (range, 1 to 20 prism diopters), and there was no significant correlation (Fisher exact test) between the magnitude of esotropia and vasculopathic etiology, posterior fossa lesion site, or isolated divergence paresis. In different positions of gaze upon a distant target, variation of esodeviation was equal or less than 6 prism diopters in 12 patients and greater than 6 prism diopters in two patients.

### DISCUSSION

Divergence paresis is an uncommon cause of acquired diplopia. Divergence paresis is associated with diverse CNS diseases (4), although in the present series, a peripheral origin for divergence paresis was proposed for patient 7, who had myasthenia gravis, a disorder that can mimic central gaze disturbances, such as internuclear

### TABLE 1. Patients with divergence paresis

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/Sex</th>
<th>Distance esotropia</th>
<th>Neuroimaging (MRI, unless otherwise stated)</th>
<th>Diagnosis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32/M</td>
<td>Esodeviation on alternate</td>
<td>Clivus mass with erosion</td>
<td>CNS lymphoma</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>62/F</td>
<td>10 PD in right/left</td>
<td>Sphenoid sinus with equivocal cavernous sinus involvement</td>
<td>Chronic lymphocytic leukemia with sinusitis</td>
<td>Developed left sixth-nerve palsy 6 weeks later</td>
</tr>
<tr>
<td>3</td>
<td>78/M</td>
<td>6 PD in right/10 PD in primary/20 PD in left gaze</td>
<td>Cerebellar atrophy</td>
<td>Wernicke ophthalmoplegia</td>
<td>Convergence insufficiency also found</td>
</tr>
<tr>
<td>4</td>
<td>79/F</td>
<td>6 PD in right esotropia in primary/10 PD in left gaze</td>
<td>Increased periventricular signal on T2 sequences, 4 x 5 mm pituitary microadenoma</td>
<td>Parkinson disease and CNS microangiopathy</td>
<td>Mild optic neuropathy OS</td>
</tr>
<tr>
<td>5</td>
<td>75/M</td>
<td>10 PD in right and primary/6 PD in left gaze</td>
<td>Atrophy and subcortical microangiopathic changes</td>
<td>CNS microangiopathy</td>
<td>History of coronary artery disease</td>
</tr>
<tr>
<td>6</td>
<td>75/M</td>
<td>2 PD in right/8 PD in left gaze</td>
<td>Atrophy, left cerebellar infarct, increased periventricular signal on T2 sequences</td>
<td>Cerebellar infarction and CNS microangiopathy</td>
<td>History of coronary artery disease, Type III DM, and hyperlipidemia</td>
</tr>
<tr>
<td>7</td>
<td>18/F</td>
<td>20 PD in right and left gaze/esotropia in primary gaze</td>
<td>Normal</td>
<td>Myasthenia gravis</td>
<td>Developed esotropia at near within 2 years</td>
</tr>
<tr>
<td>8</td>
<td>14/F</td>
<td>14 PD in right and left gaze/16 PD in primary gaze</td>
<td>Normal</td>
<td>Isolated divergence paresis</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>55/M</td>
<td>4 PD in right down gaze/2 PD in direct and left down gaze</td>
<td>Few scattered foci of increased periventricular signal on T2 sequences</td>
<td>Isolated divergence paresis</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>75/F</td>
<td>6 PD in right gaze/8 PD in primary gaze/6-8 PD in left gaze</td>
<td>Cerebellar atrophy, periventricular, and pontine microangiopathy</td>
<td>Vertebrobasilar ischemia</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>65/M</td>
<td>4 PD in right and left gaze/2 PD in primary gaze</td>
<td>Left cerebellar cryptic AVM</td>
<td>Cryptic cerebellar vascular malformation</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>31/F</td>
<td>12 PD in right, primary, and left gaze</td>
<td>Hyperintense focus in right corona radiata</td>
<td>Lacunar CVA, childhood esotropia</td>
<td>Lacunar CVA</td>
</tr>
<tr>
<td>13</td>
<td>68/M</td>
<td>6 PD in right gaze/fixation to 4 PD in primary gaze/4 PD in left gaze</td>
<td>Left ganglionic/capsular lacune</td>
<td>Lacunar CVA</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>71/M</td>
<td>4 PD in right and left gaze/fixation to 1 PD in primary gaze</td>
<td>Hyperintense signal in left frontal white matter</td>
<td>CNS microangiopathy</td>
<td>Convergence insufficiency also found</td>
</tr>
<tr>
<td>15</td>
<td>80/M</td>
<td>10 to 12 PD in right gaze/10 PD in primary gaze/fusion in left gaze</td>
<td>Cerebellar atrophy on CT</td>
<td>Isolated divergence paresis</td>
<td>Convergence insufficiency also found</td>
</tr>
</tbody>
</table>

PD, prism diopters; CNS, central nervous system; CT, computed tomography; AVM, arteriovenous malformation; CVA, cerebrovascular accident; DM, diabetes mellitus.
ophthalmoplegia (5). The condition most frequently associated with divergence paresis (found in 7 patients) was CNS microangiopathy or infarction. In contrast with Krohel's series, in which only 27% of patients had concomitant neurologic diseases (6), 80% of patients in the present series had neurologic or neuromuscular disorders. None of the patients in our study had clinical or neuroimaging evidence of increased intracranial pressure, which was a common finding in older reports (7,8).

Although prior reports have stressed the concomitance of esodeviation in all fields of gaze (4), this was not a consistent finding in the present series. In the absence of detailed measurements of esodeviation in standard positions of gaze in the overwhelming majority of reports (including reports 4, 6, 7, and 8), it is exceedingly difficult to determine the stringency of concomitance as a defining feature of divergence paresis. A minor degree of incomitance in divergence paresis was deemed acceptable in Duane's original report (1), and Bieschoswsky (9) observed that the angle of squint would increase or decrease when looking down or up, respectively. Visual target distance from the patient is critical in assessing divergence paresis, and the issue of incomitance versus concomitance may be further obscured when gaze measurements reveal esotropia for distance, fusion for near, and exotropia for test objects proximal to fusion distance because of the frequent association of convergence insufficiency with divergence paresis (9), such as was recorded in three patients in this series. Based on present (10) and past (1,9) clinical observations of gaze incomitance, pure concomitance may be regarded justifiably as a minor criterion of divergence paresis, and greater diagnostic weight should be assigned to the clinical triad of uncrossed diplopia at distance, no diplopia at near, and full versions and ductions (6).

Another widely held diagnostic tenet of disorders of divergence is that these disorders constitute a distinct entity that usually can be separated from bilateral lateral rectus muscle palsies (6). Although bilateral abducens palsies can be distinguished readily from divergence paresis by features such as limitation of abduction or esotropia at near (10), this study and others (1,11) suggest that divergence paresis and bilateral abducens palsies may be part of a continuum of esodeviation. Patients 2 and 7 developed lateral rectus palsies following initial presentation with divergence paresis. Similarly, Duane's (1) original description noted that "bilateral abducens paralysis may be converted into a divergence-paralysis, and, on the other hand a divergence-paralysis may pass into a paresis of the abducens." These observations support the close relationship of divergence paresis and abducens palsy but suggest a distinct class of abducens dysfunction producing the features of divergence insufficiency without other signs of sixth-nerve palsy (11).

No etiologic significance could be attributed to the magnitude of esotropia in this study. Although the quantity of esotropia was used by Duane (1) to distinguish divergence paralysis from divergence insufficiency, he too did not attempt to correlate cause with severity of esotropia. Alternatively, Duke-Elder (12) differentiated divergence paralysis from insufficiency on the basis of organic disease or functional origin, respectively, and not on the size of esotropia. The variety of criteria and vague nomenclature create an artificial and arbitrary classification that does not foster clinical precision. Consequently, this study uses the single term "divergence paresis" to identify divergence dysfunction of all magnitudes and etiologies.

Despite detailed neuroimaging in this study there was no single site of pathology to account for divergence paresis. The absence of a consistently demonstrable lesion supports the investigations of Scobee and Green (13) and others (10) who have argued against the existence of a divergence center. Although there are case reports of clinicopathologic identification of a divergence center, these cases were almost invariably characterized by a posterior fossa lesion and by evidence of increased intracranial pressure (7,8,14). In such cases, the operative mechanism may simply be raised intracranial pressure, which can produce the classic features of divergence paresis (11). With no compelling evidence for a single divergence center, alternative explanations of divergence paresis include dysfunction of multiple or diffusely distributed neural structures governing divergence, impaired inhibition of convergence mechanisms, e.g., convergence spasms (9), or defective passive antagonism of orbital structures to convergence, e.g., the elasticity theory (13). Although Mays (15) identified divergence neurons in the mesencephalic reticular formation of rhesus monkeys, a discrete nucleus for divergence in the human has yet to be unequivocally identified. Like the other proposed divergence center, Perlin's nucleus of convergence, the "divergence nucleus," may be a candidate for neurologic mythology (16). At present, clinicians should regard divergence paresis as a nonlocalizing cause of diplopia, and divergence paresis should be classified among other causes of heterotropia that defy precise neuroanatomic localization, such as skew deviation, convergence insufficiency, abduction paresis because of increased intracranial pressure, and nonparalytic strabismus.

REFERENCES


Ophthalmoplegia Associated With the Anti-Ri Antibody


Anti-Ri antibodies most often occur in patients with breast cancer and typically are associated with the paraneoplastic syndrome of opsoclonus-myoclonus-ataxia. This study reports a patient with diplopia and ophthalmoplegia. She had anti-Ri antibodies, and despite an exhaustive search for malignancy at presentation, breast cancer was not detected for six months.

Key Words: Anti-Ri antibody—Ophthalmoplegia—Paraneoplastic.

Anti-Ri is a highly specific anti-neuronal antibody that interacts with central nervous system (CNS) neurons, but does not interact with glia or other CNS cells. The Ri antigen is thought to be homologous to an RNA-binding protein expressed in the developing motor system (1). The anti-Ri antibody (anti-Ri Ab) is usually detected in patients with breast cancer (1), although it has been reported in patients with ovarian (2), fallopian (1), and small-cell lung cancer (3). Patients with anti-Ri Ab may develop the syndrome of opsoclonus-myoclonus-ataxia (OMA) (1-3). We report a patient with anti-Ri Ab who developed diplopia and ophthalmoplegia, but not nystagmus. Breast cancer was not discovered for six months, despite an exhaustive search at the onset of her disease.

CASE REPORT

A 60-year-old hypertensive woman sought treatment in January 1998 for dizziness and diplopia. Her physician believed she had a right abducens nerve palsy of viral etiology. The diplopia persisted, and she developed fatigue, generalized muscle aches, dysphagia, and difficulty chewing. Neurologic evaluation suggested bilateral abducens nerve palsies. Past medical history included asthma, degenerative joint disease, and endometriosis. She had undergone a hysterectomy in 1984, and a breast biopsy in 1990 showed cystic change. Medications at presentation were clonidine, Cardura, Bumex, and Estrace.

Results of evaluations in February 1998, including computed tomography (CT) scan and magnetic resonance (MR) imaging of the brain, lumbar puncture, edrophonium test, electromyography, anticholinesterase receptor antibody levels, chest radiograph, complete blood count, renal profile, thyroid stimulating hormone, antinuclear antibody (ANA), antistriated muscle antibody, and cardiac enzymes, were normal or negative. She was referred for neuro-ophthalmologic examination.

Additional symptoms noted in March 1998 included change in character of voice, a 10 pound weight loss, and occasional urinary incontinence. Results of vision and pupillary examinations were normal. Vertical ductions and versions were full. Abduction and adduction of each eye was almost completely absent, and there was a 10 prism dioptrc esotropia in primary position. There was no nystagmus or involuntary eye movement. Results of the Dolls maneuver were negative. There was no ptoisis or proptosis, and orbicularis strength was normal. Magnetic resonance imaging with gadolinium was repeated, and the test results were normal; 1 mm sections through the pons showed no abnormalities. Treatment with 60 mg per day of prednisone was begun for possible myasthenia gravis. Within two weeks the ophthalmoplegia had improved (Fig. 1), and by April 1998 adduction was almost normal, but abduction was still moderately abnormal. The dosage of prednisone was tapered because of fluid retention, and by May 1998 her symptoms and ophthalmoplegia were worsening. Repeat edrophonium test, single fiber electromyography, and anticholinesterase receptor antibody levels were negative. CT scan of the chest showed no thymoma.

The patient developed ataxia and dysdiadokinesis. Anti-Yo and anti-Hu antibodies were negative, but anti-Ri antibody was positive. A mammogram, breast ultrasound, and Miraluna nuclear breast scan (Dupont, Billerica, MA) showed fibrocystic change. Test results for serum cancer antigen (CA) 15-3, CA 27-29, carcinoembryonic antigen (CEA), and the human immunodeficiency virus were negative. Results of an abdominal CT, esophageal gastroduodenoscopy, and colonoscopy were negative. A gynecologic examination in the context of her previous surgery was normal. Four sessions of plas-
Anti-Ri Ab and Ophthalmoplegia

FIG. 1. Extraocular movements demonstrating almost complete left gaze palsy, moderate right abduction deficit, and mild left adduction deficit 2 weeks after prednisone was begun. A 10 prism diopter esotropia was present in primary position at distance.

Mapheresis produced no improvement in symptoms or signs. In December 1998, breast MR imaging showed a suspicious area in the right breast. Repeat mammography showed no obvious lesion. A quadrantectomy was done, and pathology showed two separate lesions. One lesion, slightly less than 1 cm was identified as an intraductal carcinoma, and a second 4 mm area of infiltrating lobular carcinoma was also seen. The patient underwent four cycles of cytoxan-methotrexate-flourouracil and is now receiving radiation to the chest. There has been no significant change in her moderate bilateral abduction and adduction deficits since the discovery and treatment of her cancer. Interestingly, her ophthalmoplegia improved with repeated attempts at right and left gaze.

Discussion

Neurologic paraneoplastic syndromes associated with autoantibodies are recognized with increasing frequency. Commonly detected antibodies include anti-Yo, anti-Hu, and anti-Ri (1,3). The malignancy may be occult; small-cell cancer of the lung (anti-Hu) and ovarian or breast cancer (anti-Yo) are most common when such antibodies are present (4). Syndromes include brainstem encephalitis and subacute sensory neuropathy associated with anti-Hu (5–8), and anti-Yo associated subacute cerebellar degeneration (6,9). Neuro-ophthalmologic abnormalities are varied and dependent on the area of brain affected. Nystagmus, gaze palsy, ophthalmoplegia, and ocular misalignment are most frequently reported (9,10).

Anti-Ri Ab is usually detected in patients with breast cancer (1). However, single case reports document an association with cancer of the lung (small cell) (3), fallopian tube (1), ovarian duct (11), and bladder (1). Anti-Ri Ab is usually associated with the paraneoplastic syndrome of OMA (1,3). However, a variety of ophthalmologic abnormalities, including torsional nystagmus, abducens nerve palsy, abnormal pursuit, upgaze palsy, and blepharospasm, have been associated with the Anti-Ri Ab. Luque et al. (1) described one patient each with nystagmus and abnormal pursuit, torsional nystagmus, and abducens nerve palsies, and blepharospasm. Escudero et al. (12) described a patient who had an upgaze palsy and eyelid apraxia but otherwise normal eye movement. Hormigo et al. (13) reported a patient with opsoclonus who developed impaired smooth pursuit and optokinetic nystagmus, abnormal vestibulo-ocular reflex, upgaze palsy, and bilateral abduction deficits. Concomitant neurologic and systemic abnormalities other than myoclonus and ataxia include dizziness, nausea, proximal muscle weakness, spastic quadriaparesis, hyperreflexia, dysphagia, dysarthria, dementia, and progressive encephalopathy and rigidity (1,12,14). Our patient presented with diplopia and mild systemic symptoms. She was found to have almost no horizontal eye movements, normal vertical eye movements, and small esotropia. Results of repeated evaluations for pontine abnormality and myasthenia gravis were negative. We believe the anti-Ri Ab was responsible for her neurologic syndrome and was initially selectively affecting horizontal gaze centers in the pons.

The pathogenesis of these paraneoplastic neurologic syndromes is unclear, but most investigators feel it is an autoimmune process (4,8,10,13). However, anti-Ri Ab may be present in the absence of cancer or neurologic disease. In three patients with OMA and anti-Ri Ab, no
malignancy was found 20 to 42 months after presentation, despite thorough evaluation, even following the results of an autopsy in one patient (3,13,14). Drlicek et al. (2) identified anti-Ri Ab in 7 of 181 patients with ovarian cancer and none of these patients developed a paraneoplastic syndrome over 2 years of follow-up. It appears that when present, the anti-Ri antibody is not always pathogenic, and the pathogenic presence of the anti-Ri antibody is not always associated with a malignancy. Moll et al. (4) investigated 23 patients with paraneoplastic syndromes associated with either anti-Hu, anti-Yo, or anti-Ri Ab. These patients were compared with 66 cancer patients without paraneoplastic syndromes and with 107 age-matched controls for the presence of systemic autoantibodies (ANA, anti-DNA, anticientromere, antinuclear protein, anti-Smith, antiasingle-stranded-A, anti-single-stranded-B, anti-scleroderma, antimitochondrial, antismooth muscle, antiparietal cell, antinuclear antibody). Moll et al. found significantly more patients with the paraneoplastic syndromes to have other systemic autoantibodies, and they speculated that a genetic susceptibility may exist.

Treatment of any paraneoplastic syndrome begins with removal of the cancer. Unfortunately, this removal often does not reverse the paraneoplastic abnormalities. Systemic corticosteroids, cyclophosphamide, intravenous immunoglobulin, and plasmapheresis have been used in patients with the anti-Ri Ab with mixed results (3,11,14). Dropcho et al. (3) reported resolution of opsoclonus during prednisone treatment in one patient. The dosage of corticosteroids was tapered over 30 months, and cyclophosphamide was used for the next year, during which the patient had no recurrent opsoclonus. Casado et al. (14) used prednisone and triazolam to treat a patient with opsoclonus, encephalomyelitis, and rigidity; eye movements were normal eleven months later. Jongen et al. (11) reported near resolution of OMA following removal of the cancer, and plasmapheresis. Fortunately, no improvement in ophthalmoplegia. Her condition worsened with subsequent higher prednisone dosages, removal of the cancer, and plasmapheresis. Fortunately, she has remained stable.

In conclusion, neurologic paraneoplastic syndromes are recognized more frequently. Our patient developed a unique brainstem syndrome characterized by an isolated horizontal gaze paresis. The responsible lesion was likely in the region of the parapontine reticular formation and the abducens nuclear complex, which are responsible for conjugate horizontal gaze. The normality of the results of MR images in this clinical situation should suggest the possibility of a paraneoplastic etiology. The paraneoplastic syndrome may precede the discovery of cancer by months or years, despite thorough evaluation. If the anti-Ri antibody is present and mammogram and ultrasound are negative, breast MR images should be obtained.

REFERENCES

Arachnoid Cyst of the Cavernous Sinus Resulting in Third Nerve Palsy

Dai Barr, F.R.C.Ophth., Mark J. Kupersmith, M.D., Richard Pinto, M.D., and Roger Turbin, M.D.

A 67-year-old man exhibited long-standing left third nerve palsy. Magnetic resonance imaging revealed a cystic lesion in the left cavernous sinus with signal characteristics typical of arachnoid cyst. Intradural cavernous sinus arachnoid cyst has not reported previously. Pathogenetic mechanisms are discussed.

Key Words: Arachnoid cyst—Cavernous sinus—Magnetic resonance imaging—Third nerve palsy.

Arachnoid cysts occur throughout the cerebrospinal axis (1) and comprise approximately 1% of all intracranial space-occupying lesions (2). In the cranial cavity, arachnoid cysts are usually solitary, associated with normal subarachnoid cisterns, found in the middle cranial fossa, and asymptomatic (1). A case of an arachnoid cyst of the cavernous sinus that resulted in a third nerve palsy is presented.

CASE REPORT

A 67-year-old man with a 20-year history of diplopia in the primary position was examined. He was aware that his left pupil had been larger than the right for approximately 20 years. He had no other neurologic symptoms; no history of head trauma, diabetes mellitus, or systemic hypertension, and was on no medication.

Examination revealed corrected visual acuities of 20/20 in both eyes, normal color vision, and full fields. There was no ptosis or proptosis. The right and left pupil diameters were 4 mm and 7 mm, respectively, and reacted briskly to light. There was 2+ underaction of the left inferior oblique, superior rectus, and inferior rectus and 1+ underaction of the medial rectus. Prism cover test in the primary position revealed a right hypertropia (RHT) of 12 prism diopters (PD) and an exotropia (XT) of 10 PD. In right gaze, there was an RHT of 16 PD and an XT of 14 PD, and in left gaze there was an RHT of 12 PD and an XT of 5 PD. In upgaze, there was an RHT of >16 PD and an XT of 10 PD, and in downgaze there was an RHT of 8 PD and an XT of 12 PD. There were no synkinetic movements of the upper lid, globe, or pupil. The remainder of the findings of ophthalmologic and neurologic examination were normal.

Based on the MRI findings, a diagnosis of left cavernous arachnoid cyst was made. In view of the chronicity and stability of the patient’s symptoms, no neurosurgical treatment was contemplated.

DISCUSSION

A mass with a cystic appearance within the cavernous sinus, viewed with computed tomography or MRI, may be pituitary adenoma, craniopharyngioma, Rathke’s cleft cyst (3), dermoid cyst (4), or hydatid cyst (5). These lesions were excluded as possible diagnoses in our patient because none of these lesions has an MRI appearance in which the cyst contents are isointense with CSF, as occurs with an arachnoid cyst. Normal diffusion-weighted imaging study suggested the mass was not an epidermoid cyst: unlike an arachnoid cyst, water within an epidermoid cyst is restricted and produces an abnormally high signal.

Arachnoid cysts may develop at any age and may be congenital, as a result of early developmental splitting of the arachnoid membrane (1), or may be acquired through infection, inflammation, or trauma (6). Communication of the arachnoid cyst with the subarachnoid space often persists, and progressive enlargement may occur because of a ball-valve mechanism (6). Arachnoid cysts are intra-arachnoidal (1,6,7), with the wall closely resembling the lining of arachnoid granulations (1). The contents of an
FIG. 1. Axial T1-weighted magnetic resonance image of the brain. A low signal cystic mass is seen in the left cavernous sinus, which is displacing the intracavernous internal carotid artery anteriorly. The posterior clinoid process is truncated.

FIG. 2. Axial T2-weighted magnetic resonance image of the brain. The intracavernous cyst contents are isointense with cerebrospinal fluid.
FIG. 3. Axial fluid attenuated inversion recovery magnetic resonance image of the brain. The signal from the intracavernous cyst contents has been attenuated to the same degree as the cerebrospinal fluid.

Arachnoid cysts may be indistinguishable from CSF or, rarely, may contain blood (2).

Arachnoid cysts usually occur in relation to the brain surface, but they may be intraventricular, intrasellar, or orbital, and approximately 10% occur in the sellar or suprasellar areas (1). We have found no prior descriptions of an arachnoid cyst occurring in the cavernous sinus. When present, symptoms depend on the location and size of the arachnoid cyst and may be the result of a local mass effect on adjacent structures, obstructive hydrocephalus, or the consequences of a space-occupying lesion. Third nerve palsy has been reported with an arachnoid cyst of the interpeduncular cistern (7,8) and with a hemorrhage into a suprasellar arachnoid cyst (9).

In the lateral wall of the cavernous sinus, the third and fourth nerves and the ophthalmic and maxillary divisions of the trigeminal nerve are all enclosed by separate arachnoidal epithelial membranes whose elements penetrate the nerve sheaths and inner dura to form arachnoid granulations within the cavernous venous sinus (10). The same is also true of the arachnoid membrane around the trigeminal ganglion in Meckel’s cave (10). It is therefore possible that, in utero, a splitting of the arachnoid membrane around the trigeminal ganglion allowed an arachnoid cyst to form. A slow increase in the mass was likely because the third nerve palsy did not manifest until the patient was in middle age.

To our knowledge, the occurrence of a symptomatic arachnoid cyst within the cavernous sinus has not been reported previously. Although rare, an arachnoid cyst should be considered in the differential diagnosis of a cystic lesion in the cavernous sinus found with an MRI.

REFERENCES
Microvascular Cranial Nerve Palsies in an Arabic Population

Mona al Saleh, M.D., and Thomas M. Bosley, M.D.

Objectives: The incidence of microvascular ocular cranial nerve palsies may be increasing with the prevalence of diabetes in the developing world. We review this problem for the first time in an Arabic population.

Materials and Methods: This is a prospective nonrandomized study of all patients with the diagnosis of microvascular cranial mononeuropathy seen in the Neuro-ophthalmology Clinic at the King Khaled Eye Specialist Hospital between September 1997 and April 1998.

Results: Forty-seven patients with microvascular palsies of cranial nerves 3, 4, or 6 were seen in this 8-month period. Compared to previous studies, this group had a stronger association with previously diagnosed diabetes mellitus, more males affected, and a longer duration of the cranial nerve palsy before complete resolution. Five patients had an unusual clinical course that included a second microvascular cranial mononeuropathy before the first palsy completely resolved.

Conclusions: Microvascular cranial nerve palsies may occur more frequently in this Arabic population than elsewhere and may have certain unusual features.

Key Words: Abducens nerve—Arabic population—Cranial nerve palsy—Diabetes—Oculomotor nerve—Trochlear nerve—Vascular risk factors.

Microvascular cranial nerve (CN) palsies are one important manifestation of small vessel atherosclerotic disease (1). Because vascular risk factors, particularly diabetes mellitus, are a growing health problem in developing countries (2-5), we decided to investigate the frequency and characteristics of microvascular CN palsies at the largest eye facility in the Middle East. Descriptions of microvascular CN palsies are scarce in the developing world, and the prevalence and features of this problem have not been reported in an Arabic population.

MATERIALS AND METHODS

This study was performed at the King Khaled Eye Specialist Hospital (KKESH), a tertiary ophthalmologic center with approximately 100,000 outpatient visits per year from all portions of Saudi Arabia (6). The enrollment period for this study was September 1997 to April 1998, with a follow-up period extending through November 1998. Inclusion criteria were 1) presentation to the KKESH Neuro-ophthalmology Service during the enrollment period with an isolated palsy of CN 3, 4, or 6 without pupillary involvement, orbital signs, or other recent neurologic history; 2) maximum neurologic deficit within 2 weeks of onset and complete resolution of the motility abnormality during the enrollment or follow-up period without treatment; 3) a history of vascular risk factors including diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, or age >60 years; and 4) no history or evidence of a medical problem implying another possible etiology of diplopia, such as trauma, stroke, myasthenia gravis, thyroid eye disease, malignancy, or vasculitis.

During the enrollment period, 60 patients were seen with diplopia possibly caused by isolated CN palsies. Excluded from the study group were three patients who were lost to follow-up before the diagnosis was definite, two patients whose eye motility abnormality did not resolve sufficiently during the enrollment or follow-up period, three patients who were diagnosed with nasopharyngeal cancer, one patient with probable recurrent complicated migraine, one patient with active systemic lupus erythematosus, two patients with probable ocular myasthenia gravis, and one patient with a history of mononeuritis multiplex affecting peripheral nerves elsewhere as well.

An additional 22 patients returned for follow-up appointments during the enrollment period with a previous history of resolved microvascular CN injuries well documented in hospital records. The characteristics of this group (age, sex, incidence of diabetes, distribution of CN injuries, duration of symptoms, etc.) were very similar to those of patients presenting with acute microvascular CN injuries. These patients were excluded because they did not experience acute cranial mononeuropathies during the enrollment period.

Each study patient received a complete ophthalmologic and neurologic examination. A focused history was taken and hospital records were reviewed for evidence of previous resolved CN palsies or other small vessel disease (such as diabetic retinopathy or nephropathy). Blood testing was performed on every patient, including...
TABLE 1. Demographic and clinical data

<table>
<thead>
<tr>
<th></th>
<th>Single</th>
<th>Multiple</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (no.)</td>
<td>41</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td>Acute palsies (no.)</td>
<td>41</td>
<td>12</td>
<td>53</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>20-95 (59.9)</td>
<td>44-72 (57.9)</td>
<td>20-95 (59.9)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>3:1:1</td>
<td>6:0</td>
<td>3:7:1</td>
</tr>
<tr>
<td>Right:left</td>
<td>0.78:1</td>
<td>1:1</td>
<td>0.88:1</td>
</tr>
<tr>
<td>DM (%)</td>
<td>0%</td>
<td>83%</td>
<td>8%</td>
</tr>
<tr>
<td>Duration of palsy (wks)</td>
<td>4-36 (12.3)</td>
<td>4-28 (14.6)</td>
<td>4-36 (12.4)</td>
</tr>
<tr>
<td>CN 2 (percent of presentations)</td>
<td>14 (34%)</td>
<td>3 (25%)</td>
<td>17 (32%)</td>
</tr>
<tr>
<td>CN 3 (percent of presentations)</td>
<td>2 (5%)</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>CN 4 (percent of presentations)</td>
<td>25 (61%)</td>
<td>6 (50%)</td>
<td>31 (60%)</td>
</tr>
<tr>
<td>CN 6 (percent of presentations)</td>
<td>2 (17%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; CN, cranial nerve.
* Facial palsy was not one of the inclusion criteria for this study. These two patients developed facial palsies after an initial palsy of the 6th cranial nerve.

Westergren erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), and VDRL. Neuroimaging, including computed tomographic (CT) scanning, magnetic resonance imaging (MRI), or both, was performed on 64% (30 of 47 patients).

RESULTS

The demographic characteristics of the study group are summarized in Table 1. Forty-one patients presented during the enrollment period with an isolated acute CN palsy meeting the above criteria ("Single" column). Two of these patients had a prior history of a resolved 6th CN palsy, whereas six patients had a previous history of one or more Bell's palsy and an examination demonstrating varying degrees of recovery of facial strength with aberrant regeneration.

One patient was seen during the enrollment period with an abduction deficit on the left and the complaint of recent onset of diplopia and mildly reduced vision OS. When first seen, he had excellent visual acuity OS with a mild afferent pupillary defect and nerve fiber bundle visual field loss on that side. During the next several months, he developed mild optic disk pallor while his left abduction deficit resolved completely, implying that his left optic nerve and 6th CN may have undergone a simultaneous microvascular injury. Figure 1 shows this patient's right Humphrey visual field, and this patient is also included as Patient 1 in Table 2.

Five other patients were seen during the enrollment period with microvascular cranial nerve palsies that resolved completely during the study period; in addition, each of these patients developed a second cranial mononeuropathy during the study period, as detailed in Table 2 (patients 2–6) by date of onset of initial symptoms. These patients were evaluated with CT scan (five patients), vasculitis and coagulopathy blood studies (five patients), lumbar puncture (two patients), and Tensilon test (two patients), all of which were unremarkable. The second CN palsy also resolved completely except for aberrant regeneration of a facial nerve palsy (patient 5). This group met the inclusion criteria for this study and was demographically similar to the larger group with single microvascular CN palsies. Therefore, the group was included in the analysis of Table 1 ("Multiple" column).

Table 3 details vascular risk factors in the study group and shows that diabetes mellitus was the most common atherosclerotic risk factor, encountered in 81% of patients. Duration of diabetes ranged from 6 months to 25 years, with an average duration of 12.7 years. Diabetic complications such as retinopathy and nephropathy were quite common. Hypertension was present in 28% of the study group, whereas diagnosed hyperlipidemia and coronary artery disease were less frequent. Twenty-one patients (44%) had some degree of ipsi-
lateral periorbital pain at the time of onset of their cranial nerve palsy. One patient had a previous history of an internuclear ophthalmoplegia in 1992 that was thought to be caused by a pontine infarct. Neuroimaging in the study group was significant only for age-related changes. Three patients had an ESR elevated above 60. One of these patients had diabetic nephropathy, whereas another had arthritis and the third underwent a normal temporal artery biopsy. None of these patients developed symptoms or visual sequelae of giant-cell arteritis. Other blood testing was unremarkable in the study group.

**DISCUSSION**

The isolated cranial nerve palsies reported here meet the accepted diagnostic criteria for microvascular injury to cranial nerves 3, 4, and 6 (7-11) with abrupt onset (often with periorbital pain) and spontaneous resolution of an isolated mononeuropathy in patients with no probable etiology other than microvascular atherosclerotic injury. This group of patients was similar to previous reports (7-10,12,13) with age at onset of approximately 60 years, a high incidence of right and left eyes, and comparable distribution of cranial nerve injuries (6th > 3rd > 4th). Eye motility abnormalities resolved spontaneously, and subsequent follow-up did not reveal an alternative diagnosis. In particular, there was no history of malignancy or systemic inflammatory disease, no variable or generalized weakness that might imply myasthenia gravis, and no associated neurologic signs that accompany a stroke or less common neurologic phenomena such as chronic meningitis or the Miller Fisher variant of Guillain Barré syndrome. Neuroimaging, blood testing, and studies such as lumbar puncture tailored to the clinical setting did not bring to light additional information.

Some differences were present between the group described here and previous reports. Compared to previous studies, we found substantially more men than women (more than 3:1 male:female ratio versus approximately 1:1), more diabetic patients (approximately 80% diabetic patients versus less than 50%), and a somewhat longer duration of the resolution phase (average duration of 3 months and maximum of 7 months versus a maximum of 3 months). Demographics of the patient population of this hospital do not explain these differences. Approximately one-third of the patients seen at this medical center are diabetic, but this proportion is probably equal in other major eye facilities in the world. The sex ratio of patients is equal in the hospital as a whole. Further studies are planned to evaluate this patient population more carefully for evidence of vascular risk factors, subclinical coagulopathy, and/or vasculitis.

Microvascular cranial nerve palsies may be more frequent in Saudi Arabia than appreciated elsewhere. The series of Mayo Clinic studies covering 44 years (10,14-16) included 646 patients with microvascular cranial nerve palsies, or approximately 15 patients per year at a major referral center. The current study enrolled three times as many patients in less than a year. Referral patterns to different facilities are impossible to compare, but this striking difference raises the possibility that microvascular mononeuropathies may be more common in this Arabic population than in previous reports.

The occurrence of multiple microvascular cranial nerve injuries in a subpopulation of patients is also noteworthy. Simultaneous microvascular injury to multiple cranial nerves has been reported previously (8,9,12,13,17-24). Some of these reported patients have had severe visual loss with VF defects typical of ischemic optic neuropathy (12,21). Jabs and colleagues (21) reported

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**TABLE 2. Multiple cranial nerve palsies**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Risk factors</th>
<th>Side</th>
<th>CN</th>
<th>Date</th>
<th>Resolution</th>
<th>Duration (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>DM</td>
<td>L</td>
<td>6</td>
<td>12/97</td>
<td>Complete</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>DM</td>
<td>L</td>
<td>6</td>
<td>10/97</td>
<td>Complete</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>M</td>
<td>Previous right Bell palsy</td>
<td>L</td>
<td>7</td>
<td>11/97</td>
<td>Ab. regeneration</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td>DM; HBP</td>
<td>R</td>
<td>3</td>
<td>10/97</td>
<td>Complete</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>DM</td>
<td>R</td>
<td>6</td>
<td>11/97</td>
<td>Complete</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>M</td>
<td>DM</td>
<td>L</td>
<td>3</td>
<td>12/97</td>
<td>Complete</td>
<td>24</td>
</tr>
</tbody>
</table>

CN, cranial nerve; M, male; F, female; DM, diabetes mellitus; HBP, hypertension; R, right; L, left; Ab. regeneration, aberrant regeneration.

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<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38</td>
<td>81</td>
</tr>
<tr>
<td>Diabetic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Oral agents</td>
<td>21</td>
<td>55</td>
</tr>
<tr>
<td>None</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Diabetic complications</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

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histology of one patient in which the optic nerve injury had the appearance of ischemic infarction, presumably because of microangiopathic injury similar to that reported to cause 3rd CN injury (1,25). Interestingly, the patient in the current series had much milder visual loss, although his optic nerve injury was also permanent.

Recurrent CN palsies involving the oculomotor nerves have been reported less frequently, particularly recurrent palsies occurring during a brief period. Table 4 includes all previously reported patients of which we are aware who experienced recurrent microvascular palsies, emphasizing those patients experiencing two palsies during a period of 4 months or less, similar to our patients. No previous report contains more than two such patients, whereas in the current series, five patients meeting these criteria were evaluated in an 8-month enrollment period, implying that rapidly recurrent palsies, and perhaps microvascular CN palsies in general, are more frequent in Saudi Arabia. A relatively high incidence of small vessel atherosclerotic disease might be expected because the prevalence of diabetes mellitus has increased dramatically in recent years in Saudi Arabia (4) and in much of the Middle East (3). Other vascular risk factors such as obesity, high-density lipoprotein cholesterolemia, and hypertriglyceridemia are also becoming more prevalent (5) and are expected to increase in frequency as the population ages.

Sergott et al. (22) observed in 1984 that microvascular cranial neuropathies are almost always isolated and that exceptions to this rule, either more than one motor nerve palsy per eye or simultaneous bilateral cranial palsies, make an investigation mandatory for other possible etiologic mechanisms including myasthenia gravis, giant cell arteritis, thyroid eye disease, Miller Fisher variant of Guillain Barre, neoplasm, basilar artery aneurysm or occlusion, and chronic meningeval inflammation. They suggested that the diagnostic evaluation for patients with multiple simultaneous or sequential cranial nerve palsies should include neuroimaging, ESR, forced duction testing, Tension test, glucose tolerance test, and cerebrospinal analysis.

Our experience with the current patient population suggests that, under certain circumstances, multiple cranial nerve palsies may not be a sign of undiagnosed serious medical problems. The following protocol would be appropriate for the diagnosis and follow-up of the current patient population with microvascular palsies of cranial nerves 3, 4, and 6:

1. A patient meeting the diagnostic criteria listed above should have a test for syphilis and an ESR drawn to evaluate the possibility of giant-cell arteritis (which may be less frequent than in other populations). Additional evaluation appropriate for the clinical scenario should be performed if the patient does not have atherosclerotic risk factors or if there is a history or suspicion of additional serious medical problems such as immunosuppression, infection, or malignancy.
2. The patient should be followed carefully to confirm that resolution of the neurologic deficit begins within 4-6 weeks and that the deficit resolves completely in less than 5-7 months. Any patient who deviates from the expected clinical course requires a complete evaluation tailored to the clinical situation.
3. If a second cranial nerve palsy develops before complete resolution of the first cranial nerve injury, the patient requires neuroimaging and blood testing that includes at least ESR, ANA, and tests for syphilis. More testing than this is probably not necessary if the second cranial nerve involved is 3, 4, 6, or 7, and if resolution of both cranial nerve palsies continues in a fashion compatible with microvascular injury. This clinical situation obviously requires careful follow-up and additional testing, such as suggested by Sergott et al., if the patient deviates from a course compatible with simultaneous or sequential microvascular cranial nerve injuries.

Acknowledgment: Dr. Al Saleh was supported by a grant from the Kuwait Ministry of Health.

REFERENCES

Intracranial Fatigable Ptosis

Yi-Feng Kao, M.D., Min-Yu Lan, M.D., Min-Shon Chou, M.D., and Wei-Hsi Chen, M.D.

Two patients sought treatment for bilateral fatigable ptosis; one patient had a hematoma, and the other patient had an intracranial metastasis. Compression of the central caudal nucleus in the dorsal midbrain is proposed as the cause of this ptosis, and an alteration of central acetylcholine neurotransmission may contribute to ocular fatigability. Because symptoms that suggest fatigable ptosis can be similar to those that suggest ocular myasthenia gravis, a careful evaluation is necessary to avoid misinterpretation.

**Key Words:** Fatigue—Midbrain—Ptosis.

Fatigable ptosis usually is considered a symptom of myasthenia gravis (MG) rather than an anatomic lesion (1-3). We describe two patients with fatigable ptosis that mimicked myasthenia, but that was found to be an intracranial mass lesion.

**CASE REPORTS**

**Case 1**

A 31-year-old man had acute onset of bilateral ptosis, which was associated with transient double vision on right gaze and a left temporal throbbing headache. Ptosis was less pronounced in the morning, worse at night, deteriorated after effort, and improved after rest. The width of the palpebral fissures was 8 mm on awakening, 5 mm after rest at noon, and 3 mm after 2 minutes of sustained upward gaze. A transient over-elevation of the left eyelid (Cogan lid twitch) was seen when both eyes returned to the primary position after a sustained down-gaze. There was no proptosis, conjunctival congestion, or retrobulbar pain. Visual fields were full. Pupils were equal and reactive. Eye movements were normal and conjugate. Higher cortical functions, cranial nerves, brainstem reflexes, and sensation were intact. Neostigmine produced widening of the palpebral fissures to 9 mm. However, results of the repetitive stimulation test, acetylcholine receptor antibody, and chest computed tomography (CT) were negative. Brain CT and magnetic resonance imaging (MRI) (Figs. 1A and 1B) showed a hematoma in the left cerebellar hemisphere and a peduncle compressing the ipsilateral pons and dorsal midbrain. The hematoma appeared to exert upward pressure on the midbrain. Cerebral angiography revealed no vascular anomaly. Complete blood count, blood chemistry assessment, coagulation factors, lipid profile, and test results for lupus and immunology were normal. Osmotherapy was initiated. The ptosis resolved within 3 months.

**Case 2**

A 75-year-old man had progressive development of bilateral ptosis over 3 months. His medical history included diabetes mellitus. Ptosis was less pronounced in the morning, worse at night, deteriorated after effort, and improved with rest. The palpebral fissure width was 4 mm on awakening in the morning and less than 2 mm at noon. Complete ptosis occurred after 2 minutes of a sustained upgaze. Cogan lid twitch was observed. There was no proptosis, conjunctival congestion, or retrobulbar pain. Visual fields were full. Pupils were equal and reactive. The patient showed right dysmetria, truncal ataxia, and generalized hyporeflexia. Higher cortical functions, cranial nerves, brainstem reflexes, and sensation were intact. Neostigmine produced widening of the palpebral fissures to 4 mm. However, findings of the repetitive stimulation test, acetylcholine receptor antibody, and chest CT were negative. Brain MRI showed several hyperintense lesions scattered throughout the brain, including a 2 cm x 2 cm Gadolinium-enhancing mass that compressed the left dorsal midbrain (Figs. 2A and 2B). Ptosis was presumed to be caused by compression of the dorsal midbrain by an intracranial metastasis. Complete blood count, blood chemistry assessment, and lipid profile were normal, but carcinoembryonic antigen (24.0 ng/ml) and cancer antigen-130 (120 U/ml) levels were elevated. The patient refused further diagnostic workup. Two months later, he had an acute episode of bloody emesis and gastric adenocarcinoma, which was diagnosed by stomach biopsy. He died 3 weeks later from septic shock and pneumonia.

**DISCUSSION**

Only 8 cases previously have been reported of fatigable ptosis caused by intracranial lesions (4-7) (Table 1);
our cases raise this total to 10. These 10 cases include 6 men and 4 women, ranging in age from 16 to 77 years (average, 48.4 years). In contrast to the acute onset with hemorrhage in our Case 1, intracranial tumors produce progressive fatigue, reflecting gradual expansion of the lesion. All 5 patients with unilateral fatigable ptosis had parasellar lesions, whereas the 5 patients with bilateral fatigable ptosis had dorsal brainstem lesions. This suggests a neuroanatomic distinction between lesions affecting the oculomotor nerve underlying ipsilateral ptosis and lesions affecting the central caudal nucleus in the midbrain underlying bilateral ptosis.

Although ptosis can result from central lesions involving the parieto-occipital or frontal cortex, fatigable ptosis has been seen with central lesions only when the lesions affect the midbrain (1,9), implicating the central caudal nucleus, which gives rise to bilateral efferents to levator palpebrae (8).

The mechanisms for fatigue remain controversial. A decrease of acetylcholinesterase at the motor end plate can explain the fatigable ptosis caused by the parasellar lesions damaging the oculomotor nerve. Acetylcholinesterase inhibitor reverses ptosis, and results of the repetitive stimulation test show a significant decrement in the series of Moorthy et al. (7). Administration of acetylcholinesterase inhibitor can enhance acetylcholine neurotransmission and ameliorate weakness, producing false-positive results in other neurologic diseases such as amyotrophic lateral sclerosis (11). False-positive edrophonium or physostigmine test results with brainstem lesions have been obtained from the patients of Dirr et al. (4) and in our patients, implicating a disturbance of acetylcholine. Ragge and Hoyt (5) hypothesized a disor-
TABLE 1. The summary of intracranial fatigable ptosis in the English literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Biology</th>
<th>Onset</th>
<th>Location</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Bilateral ptosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dirr et al., 1989</td>
<td>19</td>
<td>Female</td>
<td>Glioma</td>
<td>Progressive</td>
<td>MB</td>
<td>Unknown</td>
</tr>
<tr>
<td>Straube &amp; Witt, 1990</td>
<td>67</td>
<td>Male</td>
<td>Tumor</td>
<td>Progressive</td>
<td>Pons-CBM</td>
<td>Improve</td>
</tr>
<tr>
<td>Ragge et al., 1992</td>
<td>16</td>
<td>Female</td>
<td>Glioma</td>
<td>Progressive</td>
<td>MB</td>
<td>Improve</td>
</tr>
<tr>
<td>Kao et al., present study</td>
<td>31</td>
<td>Male</td>
<td>Hematoma</td>
<td>Acute</td>
<td>MB</td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>Male</td>
<td>Meningioma</td>
<td>Progressive</td>
<td></td>
<td>Improve</td>
</tr>
<tr>
<td>II. Unilateral ptosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moorthy et al., 1989</td>
<td>51</td>
<td>Female</td>
<td>Meningioma</td>
<td>Progressive</td>
<td>R sph. ridge</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Male</td>
<td>Chondrosarcoma</td>
<td>Progressive</td>
<td>R CavS</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Male</td>
<td>Meningioma</td>
<td>Progressive</td>
<td>L CavS</td>
<td>Persist</td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>Male</td>
<td>Meningioma</td>
<td>Progressive</td>
<td>R sph. ridge</td>
<td>Persist</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>Female</td>
<td>Meningioma</td>
<td>Progressive</td>
<td>R CavS</td>
<td>Improve</td>
</tr>
</tbody>
</table>

MB, midbrain; CBM, cerebellar brachium; R, right; sph, sphenoid; CavS, cavernous sinus; L, left.

ordered central control of motor units. Further investigation is needed to determine whether a central defect of acetylcholine metabolism accounts for fatigue. Brain tumors may produce variable ptosis also because of changes in size from reflexive vasodilation during sleep, when carbon dioxide is retained (10).

Clinical discrimination of fatigable ptosis from brain lesions rather than from MG may be difficult. For example, the lid twitch sign (12) of MG is seen with brain lesions (5). Although edrophonium or physostigmine tests can have positive results with intracranial fatigable ptosis, the test results for serum acetylcholine receptor antibody and the repetitive stimulation test are negative. However, these tests also may show negative results in cases of ocular MG. On the other hand, when neurologic deficits such as oculosympathetic dysfunction, focal weakness, or sensory abnormalities are found in a patient who has fatigable ptosis, an intracranial lesion should be suspected.

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Horner Syndrome due to Giant Cell Arteritis. Pas- 
cual-Sedano B, Roig C. J Neuroophthalmol 1998;20: 
75-7.

Postganglionic Horner syndrome is often associated 
with carotid artery dissection or compressive lesions 
in the upper thoracic aperture. Giant cell arteritis is a rare 
cause of this entity. This article adds one more—and a 
rare one—to the differential diagnosis of a droopy eyelid 
with a miotic pupil.

Stage-Dependent Efficacy of Intra-arterial Fibrino-
ysis in Central Retinal Artery Occlusion (CRAO). 
Schmidt D, Schumacher M. J Neuroophthalmol 1998; 
20:125-41.

Central retinal artery occlusion (CRAO) is a “bad dis-
ease,” leading to legal blindness in the majority of the 
affected eyes. Intraarterial fibrinolysis (IF) has become 
a promising therapeutic approach if applied early enough 
after CRAO. Schmidt and Schumacher looked at the ef-
cicacy of stage-dependent intraarterial fibrinolysis in 46 
patients. The signs of CRAO were allotted to three dif-
ferent stages: I—incomplete CRAO; II—subtotal 
CRAO; and III—CRAO with choroidal hypoperfusion 
(or with choroidal infarction). The amount of urokinase 
that was supplied through the femoral artery ranged be-
tween 200,000 and 1.3 million IU. Eleven patients (24%) 
showed marked improvement or recovered their vision 
completely. Seventeen (37%) showed partial improve-
ment. Fourteen (30.4%) remained stable, whereas visual 
acuity deteriorated in 4 (8.7%). IF was most successful in 
patients who had slight edema of the central retina and 
who were treated within a time window of 14 hours after 
the onset of visual loss.

Presumed Ocular Bartonellosis. Kerkhoff FT, Os-
sewaarde JM, de Loos WS, Rothova A. Br J Ophthalmol 
1999;83:270-5.

This article reviews the course of 13 patients with 
presumed ocular bartonellosis. Three of 13 had no ani-
mal exposure. Nine patients were found to have neuro-
retinitis and four had panuveitis with positive titers 
against Bartonella henselae. The cutoff for a positive B. 
henselae serology was >1:900 for the IgG and >1:250 for 
the IgM. As a common feature, all patients had patho-
logic fluorescein leakage of the optic disc. Most patients 
were treated with a combination of doxycycline and 
rifampicin, although the efficacy of antibiotic medica-
tions is not firmly established. At a follow-up of 6 
months, 17% of the affected eyes had a visual acuity of 
<20/100 because of optic atrophy and cystoid macular 
edema. Visual acuity improved two or more Snellen lines 
in 53% of the affected eyes.

Type of book: This book is a multiauthored review of current interventions and strategies for the treatment of acute ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.

Scope of book: This book provides an overview of current treatment for acute stroke useful for both medical and surgical specialists, including neurologists, neurosurgeons, intensivists, radiologists, and emergency physicians.

Contents: The book consists of 12 chapters, with the first three devoted to stroke mechanisms, classification, and general management strategies. The remainder of the book is equally divided between medical management (e.g., thrombolysis, neuroprotection) and surgical/endovascular interventions (e.g., decompressive craniectomy, hematoma evacuation, aneurysmal repair).

Strengths: This book successfully blends the authors' wealth of clinical expertise and the growing body of data from recent clinical trials. General measures of acute stroke care are described clearly in the initial chapters, with appropriate references to the literature when available. The chapter on geographic stroke units is informative and often omitted from texts of this kind. The detailed recommendations on how to manage a potential organ-donor in Chapter 2 are also rarely seen in textbooks on stroke.

Sections discussing controversial topics, such as indications for thrombolytic therapy or the use of heparin in ischemic stroke, are well balanced and well referenced. The chapters on reperfusion and neuroprotection are particularly strong. Each chapter is supplemented by numerous summary tables and imaging studies. The reproductions of computed tomographic, magnetic resonance and angiographic images are clear, helpful, and located in relevant sections of the text.

Weaknesses: Like many multiauthored texts, the writing styles in this book vary significantly across chapters. Sections in some chapters are written in the first person, which also results in awkward transitions. Finally, the title of the book suggests that the primary emphasis is on surgical and endovascular interventional techniques; the book actually offers a much broader overview of stroke care that may leave some readers either pleasantly surprised or mildly disappointed.

Recommended audience: This book will appeal to clinicians who care for patients with acute ischemic stroke. Medical students and residents will find this book useful because of the clear writing style and broad coverage of related topics. More experienced clinicians will enjoy the crisp review of the current literature.

Critical appraisal: This book successfully achieves the authors' goal of underscoring the need for acute intervention in patients with stroke; it also succeeds in describing how to do it.

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University of Rochester School of Medicine and Dentistry
Rochester, New York


Type of book: This internationally multiauthored text addresses the interactions of the immune and nervous systems.

Scope of book: This book is designed to provide information with regard to quickly evolving concepts and clinical applications of neuroimmunology. The editors went to foster interactions between basic scientists and clinicians, thereby advancing this emerging discipline.

Contents: The book begins with a review of basic principles including autoimmunity, immune interactions within the nervous system, neural regulation of the immune system, viral-immune effects on the nervous system, and strategies of immunotherapy. The remainder of the book applies these concepts to neurologic disease and injury, divided into central nervous system (CNS) and peripheral nervous system (PNS) disorders. The CNS sections elucidate neurologic disorders with cellular immune-mediation as the underlying cause (multiple sclerosis, acute disseminated encephalomyelitis), as well as humoral immune-neural interactions (paraneoplastic syndromes). Chapters are also devoted to infectious (human immunodeficiency virus, human T-cell lymphotrophic virus type I, Lyme), neoplastic and CNS vasculitic disorders. The PNS-directed discussions include acute and chronic inflammation, as well as antibody-mediated neuromuscular junction disorders. The book ends with chapters on inflammatory myopathies and how the immune response contributes to regeneration of tissues.

Strengths: The text is uniformly organized despite multiple authors. It provides an excellent review of advanced concepts in immunology and makes use of cartoon diagrams to assist immunologically challenged
readers. Each chapter begins with a background of immune-mediated issues and pathogenesis and progresses to a clinical discussion including treatment modalities and their rationale. For the neuro-ophthalmologist, the chapter on multiple sclerosis provides an excellent perspective on the ongoing controversies related to the autoimmune pinnings of the condition. Of interest is a proposed mechanism explaining the possible long-term effect of intravenous corticosteroids on the evolution of MS. The discussions on the animal model of cell-mediated immune disease, experimental autoimmune encephalomyelitis, have importance regarding the pathogenesis of many autoimmune diseases. The book is current and well referenced. The chapter on CNS tumors exemplifies much of the book, beginning with an in-depth explanation of the molecular interactions between tumor cells and the immune system. This is followed by therapeutic modalities of the future including vaccination, immuno-gene therapy, and an addendum written near press time updating the author’s hypothesis and including the most recent research into 1997. There is an excellent algorithm for the treatment of vasculitic neuropathies (chapter 21), and the discussions of clinical entities uniformly contain treatment recommendations or references to comprehensive reviews.

Weaknesses: This is an advanced text. For those not well versed in the terminology and the most recent molecular tools, the details found in some chapters can be daunting. As expected with a multiauthored text, the depth of immunologic science and clinical topics varies between topics.

Recommended audience: This text is geared toward basic scientists and clinicians interested in gaining more information on this topic. It will be of interest mainly to neurologists treating patients with neuroimmunologic diseases.

Critical appraisal: Most neuro-ophthalmologists will be drawn to the relevant and clinically oriented chapters. However, I found myself becoming more absorbed in some of the cutting-edge basic science discussions; the editors have fulfilled their goal of furthering interchange between basic and clinical scientists. This book serves as a foundation for understanding the coming decades of new immune-based therapies of neurologic disease.

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Type of book: This is a multiauthored textbook, with more than 100 contributing authors and 11 section editors. The editors contribute to 2 of the 47 chapters.

Scope of book: The book is designed to appeal to any practitioner caring for patients with cancer of the nervous system, and would appeal to the neuro-ophthalmic community as well.

Contents: The text is divided into five sections: basic principles of diagnosis and treatment, benign tumors, malignant brain tumors, metastatic disease to the central nervous system, and basic science of tumors. The section on metastatic disease is only three chapters, and so the text has a clear emphasis on primary central nervous system tumors.

Strengths: Many chapters are authored by respected experts in their subspecialties. Additionally, the chapters cover a broad array of topics and admirably include the psychosocial issues often overlooked in texts, yet so germane to the practitioner. The color plates in the center of the textbook are nicely done. The pathology slides are especially well done and illustrative.

Weaknesses: Although comprehensive, the text is heavily weighted to primary brain tumors and gives less coverage of metastatic disease as well as the peripheral nervous system. There could also be more depth regarding the systemic complications of brain tumors and their treatment; the chapter on chemotherapy needs to be expanded in this regard. As with any multiauthored text, chapter styles differ. There is a paucity of intraoperative gross pathology color plates, which would have added an additional dimension to the text. Finally, the type of paper chosen for the text does not lend itself well to the black and white imaging quality; hence, some pictures lack clarity.

Recommended audience: This text is best for practitioners who see patients with neurooncologic diseases. This would include ophthalmologists and neuro-ophthalmologists. It seems less likely to appeal to basic scientists except as an overview of clinical neurooncology. It would serve as an excellent reference text for review of specific topics; the index is extensive and easily allows particular topics to be located. There are no specific chapters dealing with neuro-ophthalmologic malignancies.

Critical appraisal: Overall, this is an impressive, comprehensive neurooncology textbook that would be useful as a reference text but is too dense for “cover to cover” reading. For a neuro-ophthalmologist, the comprehensive scope of the text leaves only a minor percentage of the text directly related to that subspecialty. Use of the text for specific neuro-ophthalmic topics requires repeated referral to the index with much bouncing between chapters. However, it would serve a very useful function for the neuro-ophthalmologist who wants to review specific tumors, and their diagnosis and treatment.

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Acknowledgment from the Editor

On behalf of the Editorial Board, I would like to take this opportunity to thank you for participating in the peer review process used to select articles to be published in the Journal of Neuro-Ophthalmology. Your efforts have helped the Journal reach a respected position among similar subspecialty publications.

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Annual Update of Systemic Disease—1999:
Emerging and Re-emerging Infections (Part I)

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

In Part I of this edition of the annual review of systemic diseases, we discuss Whipple’s disease as an emerging infectious disease and review new findings in an established infectious disease, Lyme disease, that can affect the visual system. Part II, which will appear in the March 2000 issue, will discuss the emerging infections babesiosis, ehrlichiosis, and Hantavirus and will review new findings that can affect the visual system from syphilis, an established infectious disease.

WHIPPLE’S DISEASE

Whipple’s disease was first described in 1907 (1). The agent now known to cause WD, Tropheryma whipelloi, is a periodic acid-Schiff (PAS)-positive, rod-shaped bacterium, closely related genetically to the actinomycetes (2). The agent tends to accumulate within macrophages. The organism is endemic, and evidence points to it having an environmental source. As an example, in a German study, 25 of 38 (66%) waste-water samples from five sewage-treatment plants tested positive for T. whipelloi DNA (3).

Marth et al. (4) noted the predilection of the illness to strike HLA-B27-positive, middle-aged men, implying that host factors are involved in the susceptibility to what may be a ubiquitous pathogen. They commented that patients with WD have suppressed delayed-type hypersensitivity responses in vivo and decreased in vitro T-cell responses, as well as alterations in serum-suppressor factors and T-cell subpopulations. The organism seems to have a cytotoxic effect on immunoglobulin A (IgA) plasma cells but is destroyed by macrophages. It is postulated that it is this toxic effect that allows it to elude local gut immune defenses (5). Marth et al. (4,6) reported that WD patients have reduced numbers of circulating cells expressing CD11b, a cell-adhesion and complement-receptor molecule on macrophages involved in the activation of intracellular killing of pathogens.

This multisystem disorder typically features symptoms such as abdominal pain, fever, diarrhea, lymphadenopathy, and polyarthritis. Twenty percent of cases do not have gastrointestinal features, and neurologic involvement is seen in 10% of cases (7). Ocular involvement is said to occur in 2.7% of cases (8). The ophthalmic signs typically seen include uveitis, vitritis, and retinitis. Neuro-ophthalmic signs include nystagmus, optic neuritis, papilledema, gaze palsy, and ophthalmoplegia (9,10).

Systemic Manifestations

Whipple’s disease does not have to present as a gastrointestinal disorder. Schilling et al. (11) reported a series of patients who presented with a seronegative, migratory, nondestructive polyarthritis due to WD before any gastrointestinal symptoms developed.

Whipple’s disease can have a pulmonary presentation. Kelly et al. (12) reported a 31-year-old man without gastrointestinal illness whose chest radiograph demonstrated several pulmonary nodules that enlarged rapidly. The histology of the endobronchial lesions demonstrated WD. Riemer et al. (13) described a man with systemic WD with pericardial and pleural effusions and severe pulmonary hypertension. After 3 months of antibiotic treatment, there was a complete resolution, not only of the symptoms known to be associated with WD (diarrhea, arthralgia, pericardial and pleural effusions), but also the pulmonary hypertension.

Although cardiac involvement in WD has been noted, it is rare to be the main manifestation and rarely has required therapy beyond antibiotics. Schneider et al. (14) reported a case admitted because of dyspnea, fatigue, chest pain, and dizziness. Endoscopy was performed due to 6 months of diarrhea with an attendant 10-kg weight loss and revealed T. whipelloi, confirmed by both the presence of typical PAS-positive material and by polymerase chain reaction (PCR). The aortic valve was replaced after the diarrhea had resolved with antibiotic (trimethoprim-sulfamethoxazole) therapy, and histologically demonstrated, PAS-positive, rod-shaped material was thought to be the cause of the aortic insufficiency. The authors pointed out that 58% of patients with WD have clinical cardiac findings, and 76% have cardiac lesions at autopsy. These cardiac manifestations may proceed gastrointestinal involvement and may even be the sole manifestation of the illness.
Khairy and Graham (15) reported a 50-year-old man with WD and reviewed the literature on cardiac involvement. This man had severe tricuspid regurgitation and moderate aortic and mitral regurgitation. Both valvular and ventricular abnormalities were demonstrated. They reported that the cardiac manifestations of WD are myocardiitis, constrictive pericarditis, valvular deformities, coronary arteritis, and congestive heart failure. WD may also be a cause of sudden cardiac death, as recently described by McGettigan et al. (16) and Mooney et al. (17). These patients died suddenly of an unrecognized myocardiitis as part of WD.

Marinella and Chey (18) showed that the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may be seen in the course of WD, even when there is no gastrointestinal involvement, and that it may respond to antibiotic therapy.

The series of Misbah et al. (19) reminds us that the diagnosis of WD can be made if one is suspicious, even if typical gastrointestinal signs are lacking. This series describes five patients, four with atypical features of WD (immune thrombocytopenic purpura, juvenile chronic arthritis, isolated muscle weakness, and quadriaparesis), as well as one case with fever of unknown origin, who had all been investigated elsewhere and had undergone normal jejunal biopsies with no evidence of PAS-positive macrophages. Yet, when PCR analysis for \( T. \) whippeii was also performed on various tissues (including peripheral blood, lymph node, muscle, and synovium), it was positive in all patients in at least one tissue. Furthermore, PAS-positive material was seen in four of five cases in extragastrointestinal sites. This series serves to remind us that not only do patients not need to demonstrate typical gastrointestinal symptoms, but even if one has the atypical findings such as drowsiness, behavioral changes, and loss of memory; cranial neuropathy, ataxia, and pseudobulbar palsy have also been reported (24,25). A recent report of central myelopathy from WD was reported by Clarke et al. (26).

**Neurologic Manifestations**

The typical neurologic features include nonspecific findings such as drowsiness, behavioral changes, and loss of memory; cranial neuropathy, ataxia, and pseudobulbar palsy have also been reported (24,25). A recent report of central myelopathy from WD was reported by Clarke et al. (26).

**Ophthalmic Manifestations**

Many ocular manifestations of WD have been reported, including uveitis, vitritis, retinitis, myositis, papilledema, nystagmus (oculopatalal myoclonus), and optic atrophy. These typically occur in the setting of an accompanying systemic illness. That WD can have its typical ocular manifestations in the absence of the characteristic gastrointestinal symptoms is evidenced by the case of Nishimura et al. (21). This patient, whose right eye (OD) was phthisical due to prior uveitis-induced neovascular glaucoma, presented with severe acute posterior uveitis in the left eye (OS). There were no significant gastrointestinal signs; the systemic findings of fever, anemia, weight loss, rash, arthralgia, and myalgia were present. The evaluation of the anemia led to esophageogastroduodenoscopy and jejunal biopsy. PAS-positive histiocytes were seen within the lamina propria, and PCR demonstrated \( T. \) whippeii rDNA. Worsening ocular inflammation OS responded to a subtenon injection of triamcinolone, whereas the systemic findings responded to trimethoprim-sulfamethoxazole therapy. The authors pointed out that WD should be considered in the differential diagnosis of recurrent uveitis.

Williams et al. (22) reported the case of a man who presented with 5 months of bilateral granulomatous uveitis 7 months after uncomplicated bilateral cataract surgery. His medical history included a steroid-responsive arthritis and several months of fever of unknown origin. A biopsy of the remaining lens capsule was performed because of the refractory nature of what was thought to be phacoanaphylactic uveitis and yielded PAS-positive, diastase-resistant bacilli consistent with \( T. \) whippeii, confirmed by electron microscopy and PCR. Further confirmation was obtained via jejunal biopsy. Although the systemic component responded to trimethoprim-sulfamethoxazole, cefixime, rifampin, and doxycycline therapy, the resistant intravitreal inflammation required intravenous ceftriaxone to control it. The authors noted the appearance of granular crystalline deposits on the iris margin and lens capsule and thought that these, along with similar deposits that may appear on the corneal endothelium, might be a useful diagnostic sign for WD.

Sommier et al. (23) reported a case in which an isolated recurrence of WD occurred in the eye. This 63-year-old man had been treated for gastrointestinal WD 30 years before. When he presented with chronic bilateral vitritis, evaluation by jejunal biopsy was negative, but the PCR on the vitreous was positive in both eyes.
nervous system (CNS) WD and reviewed the 84 cases they found in the literature. They pointed out that historically, many cases of CNS WD are not diagnosed until after death. They reported that 80% of cases had systemic signs. Cognitive and psychiatric changes were the most common neurologic manifestations, whereas the classic signs of oculomasticatory myorhythmia and oculo- orofaciokostal myorhythmia were present in 20% of cases and were invariably accompanied by a supranuclear vertical gaze palsy. Tissue biopsy was a sensitive technique; 89% of those who had biopsies had positive results. They suggested that CNS WD should be considered in patients with unexplained systemic illness with neurologic signs, especially if supranuclear vertical gaze palsy, rhythmic myoclonus, dementia with psychiatric symptoms, or hypothalamic manifestations are seen. They recommended that patients with possible CNS WD undergo small-bowel biopsy. Unfortunately, Lynch et al. (29) showed that small-bowel biopsy, even when PCR is performed, may not detect all cases of CNS WD. They had six cases of CNS WD, four of which (67%) did not have PCR supporting the diagnosis of WD on jejunal biopsy. Similarly, De Coene et al. (30) reported a patient with a left parietal, ring-enhancing lesion on MRI, where the diagnosis of CNS WD required brain biopsy. In this case, there were no gastrointestinal symptoms, and the jejunal biopsy was negative on histopathology. Thus, even if the bowel biopsy is negative in a case of suspected CNS WD, brain biopsy should be considered.

Peters et al. (31) described a variant of neuro-WD that resembles sarcoidosis. The authors described a 53-year-old man with “sarcoidlike” WD, which included granulomas, and pointed out that these two diagnoses must be differentiated, as treatment of WD with corticosteroids because of confusion with neurosarcoidosis can lead to progressive illness. Their patient was treated with procaine penicillin G and streptomycin followed by doxycycline. There was initial improvement, a later relapse responded to ceftriaxone and cefixime.

Neuro-ophthalmic Manifestations

Simpson et al. (32) reported a case of oculo-orofaciokostal myorhythmia associated with cerebral WD. This case was unusual in that, although the patient’s mental status improved after starting intravenous ceftriaxone, resolution of the convergent-divergent pendular nystagmus associated with a synchronous, rhythmic movement of the mouth, jaw, and extremities occurred only after treatment with valproate. The authors discussed the alternative therapies of intravenous trimethoprim-sulfamethoxazole for 2 weeks followed by oral trimethoprim-sulfamethoxazole twice daily for 1 year and the option of intravenous ceftriaxone followed by oral trimethoprim-sulfamethoxazole in combination with valproate in patients in whom the abnormal movements persist.

Rajput and McHattie (33) reported a case of a progressive supranuclear ophthalmoplegia with leg myorhythmia. This patient had neither ocular nor facial myorhythmia. The neurologic symptoms developed 16 years after the onset of WD. The ocular symptoms (but not the leg myorhythmia, which responded to valproate) were refractory to antibiotic therapy or therapy for parkinsonism or tremor.

New Diagnostic Tools

The original diagnosis of WD was based on the presence of rod-shaped organisms in silver stain sections of involved tissues. In 1961, these organisms were identified as a bacteria by electron microscopy. Diagnosis has traditionally relied on the demonstration of diastase-resistant, PAS-positive granules within the histiocytes of the lamina propria of the small intestine. Although the organism has not been cultured, new diagnostic tools emerged. In 1992, a 16S rRNA gene was detected and found to be specific for WD.

Tasken et al. (35) pointed out that even when the diagnosis of WD was established by older methods, PCR may play a role. They described two cases in which therapy for WD had failed. In one, PCR demonstrated T. whippellii, and changing specific therapy was justified. In the other case, in which the diagnosis had been made by brain biopsy because the PCR was negative for WD, further diagnostic testing led to the correct diagnosis, monocye-derived histiocytosis, being established.

Mendel et al. (36) recently showed that stereotactic brain biopsy is an adequate method of obtaining tissue for the demonstration of neurologic involvement in WD. Their patient presented with nonfocal neurologic findings (lethargy, behavioral changes) with hypogonadism and weight gain. An MRI scan revealed hyperintense lesions on T2-weighted sequences in the right fornix, putamen, and hypothalamus. The right putamen was biopsied and was consistent with WD.

That PCR is more sensitive than traditional methods of detection is demonstrated by the case of Muller et al. (37), who demonstrated PCR reactivity for T. whippellii in segments of bowel that were histologically negative. They also showed that PCR was sometimes positive on peripheral blood lymphocytes but that a tissue biopsy was more reliable.

Von Herbay et al. (38) performed the PCR assay on 37 bacterial control strains and intestinal biopsy samples from 16 patients without WD and 88 intestinal biopsy specimens from samples from 35 WD patients. In no case did a control test false-positive on PCR. In every pretherapy WD specimen that was formalin fixed, DNA of T. whippellii was detected, whereas those specimens fixed in Bouin’s were negative. Treatment prompted conversion of PCR to negative in 23 of 24 cases, typically within 1 year of therapy. However, despite negative intestinal PCR, symptomatic cerebral WD was found in their patients. Thus PCR from intestinal biopsy samples may be more helpful for diagnosis than for gauging disease eradication.

As for the diagnosis of neurologic WD, von Herbay et al. (39) looked at CSF analysis in 24 patients with WD, with and without clinical neurologic disease, by cytology and PCR. Four of five patients (80%) with neurologic...
illness tested positive for WD. Those without neurologic symptoms were grouped into those tested before or after antibiotic institution. Of the “virgin” samples, 70% without neurologic symptoms were positive; once therapy was instituted, the rate of detection dropped to 27%. Thus, even in WD patients without neurologic signs, CSF analysis may be a useful diagnostic tool for detecting subclinical neurologic infection.

Singh (40) points out that despite the utility of PCR, diagnosis of WD still does not fulfill Koch’s postulates, as it was not possible to culture the bacillus

Arthrobacter

species. Thus, Arthrobacter may present with a clinical syndrome resembling WD, may have PAS-positive material on biopsy, and may be differentiated from WD by molecular analysis. Thus, if PCR on ocular material does not yield an etiopathogenesis, a search should be made for other involved tissues to sample for PCR and histology.

Besides using it as a diagnostic tool, Ramzan et al. (42) used PCR as a measure of therapeutic efficacy. He performed PCR for

Arthrobacter

in 30 stored pre- and post-treatment biopsy specimens of patients with clinically suspected and histologically confirmed cases of WD, as well as in eight patients in whom WD had been considered in the differential diagnosis but could not be confirmed upon examination of biopsy specimen(s). PCR was positive in 29 of 30 (97%) of the patients with histologically confirmed WD and in seven of the eight (87%) of the patients in whom the disease was clinically suspected. They also had small-bowel biopsy specimens from 17 of the patients treated for WD. Twelve of these 17 (71%) patients had persistent positive results on PCR. Of these 12 patients, seven (58%) either never responded or had a clinical relapse. None of the five patients whose post-treatment biopsy specimens had negative results on PCR had a relapse. Their conclusion was that a positive post-therapy PCR may prognosticate relapse, and a negative post-therapy PCR was predictive of a good outcome. These data argue for routinely obtaining pre- and post-therapy biopsy specimens for PCR.

Duprez et al. (43) reported the MRI findings in a pediatric case of neuro-WD. MRI demonstrated white matter lesions of very low signal intensity on T1-weighted with hyperintensity on proton density and T2 sequences, with some peripheral enhancement on delayed contrast-enhanced T1-weighted images. These lesions were seen to shrink with therapy.

**Therapy**

Petrides et al. (44) pointed out that clinical response to therapy may precede histologic remission. Their patient presented with weight loss, arthralgias, and diarrhea. Although the biopsy of the gastric mucosa was negative, duodenal biopsy revealed PAS-positive, foamy macrophages within the lamina propria, and bacilli typical of WD were found on electron microscopy. PCR confirmed the diagnosis, demonstrating the typical portion of the 16S ribosomal RNA gene sequence corresponding to the Whipple bacillus (

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risk of cerebral involvement and relapses. Patients with WD should be treated for 1 year with antibiotics that do not cross the blood-brain barrier. CNS relapse is resistant to treatment.

Singer et al. (40) echoed the view of Alba et al. that treatment should include antibiotics that penetrate the CSF, since there is a high incidence of unrecognized CNS involvement. He recommends daily parenteral administration of 1.2 million units of benzylpenicillin (penicillin G) and streptomycin 1 g for 2 weeks, followed by treatment with cotrimoxazole (trimethoprim 160 mg and sulfamethoxazole 800 mg) twice daily for 1 to 2 years. He also recommends PCR analysis of cerebrospinal fluid before and at the conclusion of therapy. Singer et al. (47) also reported a case of CNS WD that failed conventional therapy and responded to rifampin.

Schneider et al. (48) reported their case and a review of all cerebral WD cases that were reported in a decade (N = 15). They found that patients treated with penicillin alone had a worse prognosis than patients who also received streptomycin. Five of 12 (42%) of patients (40%) treated with trimethoprim-sulfamethoxazole did not respond. They concluded that third-generation cephalosporins were beneficial and recommended an initial regimen of ceftriaxone combined with streptomycin for CNS WD.

Williams et al. (22) reported their case of ocular inflammation in which therapy with the agent of choice, trimethoprim-sulfamethoxazole, was not possible due to drug intolerance. Cefixime, and later the combination of rifampin and doxycycline, did not eradicate the illness. In this patient, the addition of 2 g/day of intravenous ceftriaxone sodium to rifampin and doxycycline caused a marked clinical improvement.

Finally, Schneider et al. (49) reported a novel therapy for refractory WD using interferon gamma. This is based on the observation by Marth et al. (4,6) that patients with WD have reduced monocyte interleukin 12 production and decreased interferon gamma secretion by peripheral blood mononuclear cells in vitro. They postulate a genetic substrate for this defect. The patient of Schneider et al. (49) had a 10-year history of multiple antibiotic-resistant WD. Despite the absence of clinical neurologic disease, T. whipelli DNA was found in the CSF on PCR. The patient was started on a regimen of ceftriaxone/trimethoprim-sulfamethoxazole and interferon gamma. Over the next several months, clinical response was achieved, and PCR on CSF and duodenal tissue tested negative for T. whipelli.

LYME DISEASE

Introduction

Lyme disease is the most common tick-borne infection in North America with more than 70,000 cases reported between 1982 (since surveillance was begun) and 1994. The causative agent, a spirochete, Borrelia burgdorferi, is transmitted by the nymphal form of ixodid ticks that comprise the Ixodes ricinus complex. Specifically, I. scapularis (formerly I. dammini) is the vector in the northeastern (Massachusetts through Maryland) and midwestern (Wisconsin and Minnesota) part of the United States, and I. pacifica is the vector in the west (California and Oregon). Although Lyme disease has been reported in 43 states and the District of Columbia, more than 90% of cases occur in the above-mentioned endemic areas. Three genomic groups of B. burgdorferi have now been identified. B. burgdorferi sensu stricto is responsible for virtually all North American infections. The other two groups, B. garinii and B. afzelii, account for most strains found in Europe. Lyme disease usually begins in the summer since nymphal forms flourish during the months of May through July. Adults and larvae also feed on humans but are less likely to transmit the disease. There have been a number of focal epidemics occurring particularly in the northeast. A number of areas have been identified as highly endemic with attack rates between 1% and 3%. Two population-based studies of suburban communities of Westchester, NY, reported incidence rates between 2.6% and 3.0% and prevalences of 8.8% and 17% (50,51). Other areas of high endemicity include Great Island, MA, Fire Island, NY, and, of course, the region of Old Lyme, CT.

The clinical features of Lyme disease begin with the development of a characteristic expanding annular rash, erythema chronicum migrans (ECM), at the site of the tick bite, usually in the thigh, groin, or axilla. The central area turns blue and then clears. Secondary annular skin lesions also develop that may coalesce. The second stage occurs within days to weeks and may involve the CNS, heart, other skin sites, or joints. After months to years, the third stage of infection manifests. Stage 3 may occur after a long period of latency, making the diagnosis especially difficult. Ocular and neuro-ophthalmic manifestations are not common. They may include follicular conjunctivitis, nummular keratitis, uveitis including iritis (anterior, intermediate, and posterior forms including...
panophthalmitis), choroiditis and exudative retinal detachment, meningitis with papilledema, and cranial neuropathy (52). Nonspecific episcleritis and conjunctivitis occur in early disseminated disease in approximately 10% to 11% of cases. All stages of the disorder are curable with antibiotic therapy, although relapses may occur. Diagnostic testing is largely comprised of various serologic tests and assays as well as culture. The Centers for Disease Control (CDC) established a clinical definition of Lyme disease based on a combination of clinical signs and symptoms as well as results of laboratory testing (53).

Diagnostic Modalities

The classic clinical manifestation of an expanding rash after a tick bite occurring in a patient from a region of high endemicity for Lyme disease presents no diagnostic difficulty. Such a presentation carries a pretest probability of Lyme disease in the absence of any serologic testing of at least 80% as estimated by an expert panel (53). However, the clinician is not always fortunate enough to have a patient with such a presentation. Because Lyme disease is a systemic condition with protean manifestations and symptoms often occurring after a long period of latency without a history of an ECM-like rash or patient recollection of a tick bite, the diagnosis is considerably more difficult. This is especially true in those who present with late-stage presentations such as ocular or neuro-ophthalmic signs and symptoms. In these situations, the clinician will have to rely on the results of serologies to establish a diagnosis. Laboratory testing, however, often potentiates the confusion. The current laboratory modalities commonly available for diagnosis of Lyme disease include enzyme-linked immunosorbent assay (ELISA) to detect the presence of antigen-specific IgM and IgG antibodies, indirect immunofluorescence assay (IFA), antibody-capture immunoassay (EIA), Western blotting, and, for confirmation, PCR, and culture. Unfortunately, there are significant limitations of serologic and laboratory testing. The pitfalls of such testing include a false positivity rate of as high as 7% in individuals with no known exposure, lack of interlaboratory standardization, and overall poor reliability and accuracy with as many as 21% of positive samples missed. Cross-reactivity with some syphilis serologic tests adds to the difficulty and confusion (54). In addition, there are between 5% and 10% of patients with positive serology as a result of previous infection who do not have active disease, meaning that their symptoms are a result of a condition other than Lyme disease. ELISA alone only has a sensitivity and specificity of 89% and 72%, respectively. The sensitivity is even less (50%) in the early stages of infection since it takes as long as 4 to 6 weeks after infection for seroconversion to occur. Additionally, because PCR can amplify DNA from dead or live spirochetes, it cannot distinguish active from inactive disease. Specimens for culture are of low yield unless a biopsy sample is obtained from the leading edge of suspected ECM lesions (55).

The limitations of laboratory testing can unfortunately lead to both under- or overdiagnosis. The problem of overdiagnosis has been in part contributed by unwarranted enthusiasm on the part of the practitioner in assigning a Lyme disease diagnosis. This is partly related to the epidemic nature of the illness and high levels of patient awareness and anxiety regarding this condition. Thus, despite lack of firm clinical or laboratory evidence, many unnecessary treatment regimens have been administered. Reid et al. (56), at the Yale Lyme Disease Clinic, studied 209 patients with a presumptive diagnosis of Lyme disease assigned by their referring physicians and found that only 21% met their criteria for active Lyme disease. In these cases, 19% had previous infection but not active disease and 60% had no evidence of Lyme disease, active or past. Additionally, those classified as having previous disease or no evidence of disease had considerable use of health resources, had frequent minor adverse reactions, reported significant disability, and had high rates of depression and stress. It is quite apparent that specific guidelines are necessary to diminish unwarranted use of laboratory tests and inappropriate treatment. Recently the American College of Physicians established guidelines for laboratory evaluation of Lyme disease following the study of Tugwell and colleagues (57) on the use of laboratory testing in patients suspected of having this disease. They extracted clinical, epidemiological, and laboratory data by searching relevant articles in MEDLINE between 1982 and 1996. The data were used to calculate sensitivity, specificity, and likelihood ratios, and a random-effects model was used to combine the proportions from eligible studies. Three clinical scenarios were used as examples, and the predictive values of laboratory testing in each clinical situation were calculated. Guidelines were then formulated for laboratory testing of patients suspected of having Lyme disease based on the predictive values obtained. They concluded that those patients with a pretest probability of >0.80 and <0.20 should not undergo laboratory testing. In the former situation, a positive test confirms the diagnosis and a negative test only lowers the post-test probability to 0.63. Such patients should thus be treated empirically. In the latter situation, the pretest probability is so low that a positive test would more likely be a false positive rather than a true positive and a negative test would essentially rule out Lyme disease. This is true even if the patient is from a highly endemic area. Such patients should be evaluated for other diagnoses. Their analysis unfortunately did not include patients with more unusual manifestations such as neuro-ophthalmic or ocular manifestations; thus guidelines for this subset could not be established, but the authors did recommend two-step serologic testing as described previously while further studies are available. Diagnosis of neuroborreliosis requires a high index of clinical suspicion since the manifestations often occur long after clinical exposure and the symptoms may be nonspecific. Currently, the most sensitive diagnostic test is the demonstration of intrathecal antibody production. For patients with pretest probabilities between 0.20 and 0.80, sequential, serologic testing
with ELISA followed by Western blotting should be performed. This was supported by Porwancher (58) who analyzed IgM Western blot criteria by using bayesian analysis to compute the probability that the results of a patient's Western blot test represents true Lyme disease. He found that patients with low pretest probabilities of between 1% and 10% yielded post-test probabilities of 4% to 32%. Use of other assays such as T-cell proliferation responses need further validation. This assay in one study was not only positive in 11 of 12 patients with Lyme disease but also in eight of 12 normals (59). With respect to PCR assays, the published studies are insufficient to allow guidelines for their use. However, PCR assays of CSF and joint fluid may be promising.

Thus it is essential that before initiating a serologic workup, a reasonable pretest probability should be determined based on the available clinical and epidemiological data. A cost-effective analysis of various treatment strategies would hence be useful in substantiating such guidelines. This was investigated by Nichol et al. (60), who performed a cost-effective analysis of four different test strategies in patients with suspected Lyme disease. These were (i) no testing—no treatment, (ii) testing with ELISA followed by antibiotic therapy in those patients with positive test results, (iii) two-step testing with ELISA followed by Western blotting followed by antibiotic treatment in those patients with a positive result on either test, and (iv) empirical antibiotic therapy. They concluded, as did Tugwell et al. (57), that the no testing—no treatment strategy should be applied to those with a low pretest probability of Lyme disease, empiric antibiotic therapy to those with a high pretest probability, and two-step testing to those with intermediate probability. It is hoped that adherence to these published guidelines would greatly reduce the cost of unnecessary testing and prevent treatment-related complications.

Thus, it seems clear that reappraisal of existing diagnostic techniques and development of novel ones that may enhance a clinician's ability to assign or refute a diagnosis of Lyme Borelli is necessary. Currently Western blot analysis tests for a panel of antigens that are specific for Lyme infection. Engstrom et al. (61) established criteria for IgM blot positivity that require the presence of antibody for two of the following antigens: Osp C \( (24 \text{ kDa}, \text{DepmA} (39 \text{ kDa}, \text{or FlaB} \text{(flagellin, 41 kDa). An IgG Western blot is considered positive if five of ten bands are present. The greater the specificity of the separated antigens, the fewer the false-positive test results. There is accumulating evidence that a 37-kDa antigen may be important in the early IgM response. Gilmore and co-workers (62) recently isolated, cloned, and expressed this antigen and found that it was a flagellar outer sheath protein termed FlaA. A recombinant form was expressed, and sera from individuals with Lyme disease and negative controls were tested for reactivity against it. They found that 38% of Lyme disease patients tested positive, which increased to 57% when convalescent sera were assayed, but none of the controls tested positive (100% specificity). Therefore, inclusion of this putative flagellar outer sheath protein as part of a standardized panel of antigens for IgM immune antibody detection may significantly improve the specificity of Western immunoblot serodiagnostic testing.

As mentioned previously, culturing B. burgdorferi usually gives a low yield except when obtained from the margin of an ECM rash via punch biopsy. Phillips et al. (63), however, prepared a culture medium that would allow growth of cell wall-deficient organisms or L-forms. Using their technique they were able to demonstrate growth of B. burgdorferi in 43 of 47 (91%) of patients with chronic Lyme disease, in many of whom serologic testing was inadequate to make a definitive diagnosis. Positive cultures were confirmed by fluorescent antibody immune-electron microscopy using monoclonal antibody against Osp A and Osp A PCR. The specificity was 100% when healthy controls were cultured. Since a standard for an infectious disease diagnosis is a positive culture, this new method of culturing Borrelia sp may be an excellent candidate for the gold standard for laboratory diagnosis of Lyme disease.

We previously alluded that diagnosis of neuroborreliosis is more challenging. To establish a diagnosis of CNS Lyme disease, several criteria need to be fulfilled while maintaining a high index of suspicion. Exposure to the appropriate ticks in an endemic area, a compatible neurologic deficit not explainable by any other condition, and at least one of the following:

1. documented ECM rash or biopsy proven B. burgdorferi lymphocytoma or acrodermatitis chronica atrophicans,
2. intrathecal antibody production (current gold standard indicator of CNS Lyme infection),
3. other organ-system involvement with elevated serum titers of specific antibody,
4. fourfold rise in titers in paired serologic specimens,
5. histologic or PCR proof of the presence of B. burgdorferi

are necessary to make the diagnosis. Since lumbar puncture is a necessary procedure in the workup of virtually any neurologic disorder, CSF testing for Lyme antibody is critical in those patients with a reasonable pretest probability for Lyme infection. A positive test usually indicates CNS infection. On the other hand, a normal CSF should not be used to exclude Lyme disease if the clinical suspicion is high. Although serum antibody levels are usually abnormal in those with documented intrathecal production of antibody, a positive CSF assay may occur in the absence of detectable serum levels if the patient has already received antibiotic therapy but at insufficient total dosage for eradication of CNS infection or the patient is in the early stages of infection. A false-positive result may occur but happens rather infrequently (three of 77 [4%] in one study) (64,65).

**Ophthalmic Manifestations**

Most of the unusual Lyme manifestations reported in the literature in the past 2 years that involved the CNS
did not involve the visual system or the globe and its structures. However, Miyashiro et al. (66) reported a case of nummular interstitial keratitis in a 57-year-old man who had contact with freshly killed deer and later developed foreign-body sensation in his right eye. He was found to have interstitial keratitis and was initially treated for herpes simplex stromal keratitis. Systemic workup only revealed a positive Lyme ELISA (178 U/mL; normal, <159 U/mL). Although the background of this case, specifically the patient's contact with freshly killed deer, is highly suggestive of possible Lyme infection, several other factors are necessary to calculate the pretest probability of infection. Such factors include infectivity rate of the deer in the geographic location the animal inhabited, the patient's travel history to locations of high endemicity, and history of an EM-like rash or arthritis. If the demographics reveal low infectivity rate for the deer, low prevalence of Lyme borreliosis in the area, no travel to endemic regions, and no rash or other supporting systemic signs and symptoms, then the pretest probability for Lyme disease would be low. Thus, the likelihood that the positive ELISA test was actually a false-positive result would be high. Other important factors to consider in determining whether this was truly Lyme keratitis include the experience and reliability of the laboratory in assaying for Lyme antibody, results of Western blot analysis, as well as ocular and antibody titer response to antibiotic therapy.

A specific diagnosis in a uveitis patient is often lacking. Results of a workup are often unrevealing and misleading. Lyme titers are usually ordered as a part of a battery of tests despite a lack of any specific history. To assess the utility of such testing, Mikkila and co-workers (67) evaluated 161 uveitis patients who reside in endemic areas for serum antibodies to *B. burgdorferi*. They found elevated levels in 26 patients (16.1%); however, only four (2%) patients had a history that would corroborate a Lyme diagnosis due to history of a tick bite, systemic symptoms, response to antibiotic therapy, or a positive PCR result. They concluded that such nonselective testing for Lyme disease was inappropriate even in patients coming from endemic areas. This is consistent with the previously mentioned recommendations. In a subsequent paper, however, Mikkila and colleagues (68) suggested that Lyme disease should be in the differential diagnosis in patients specifically manifesting intermediate or posterior uveitis. They reported seven cases over a 1-year period in 160 consecutive patients (4.3%). Four of the seven (57%) had positive ELISA from serum or CSF and two (29%) had positive PCR from serum or CSF. Six of the patients had a clinical history compatible with Lyme disease as a result of an ECM rash or other systemic symptoms compatible with those of Lyme disease or had a clinical response to antibiotics.

**Neurologic Manifestations**

The most common neurologic manifestations of Lyme disease include cranial neuropathy, lymphocytic meningitis, and encephalomyelitis. In patients with a more indolent course a disseminated mononeuropathy multiplex or a mild encephalopathy manifesting as nonfocal cognitive or memory deficits as well as neuropsychiatric abnormalities may occur. A post-Lyme syndrome may also occur, manifest with alterations in mood and cognition, in addition to symptoms of fatigue.

Kan et al. (69) recently reported a case of pseudotumor cerebri in an 8-year-old child manifesting with acute onset headache, papilledema, and sixth nerve palsy. She was treated with ceftriaxone for 4 weeks and acetazolamide with reduction in CSF opening pressure and resolution of papilledema and diplopia. A mild residual abducens nerve palsy remained at 2 months after treatment. Twelve other cases were reviewed; however, 11 of 12 patients presented with systemic findings and signs of Lyme disease before the development of pseudotumor cerebri. Overall the authors report an excellent prognosis for Lyme-associated pseudotumor cerebri. Corticosteroids, serial lumbar punctures, shunt procedures, and other diuretics have not been used in this form of pseudotumor cerebri.

Kobayashi et al. (70) described a case of an unusual form of encephalomyelitis in a 36-year-old Japanese woman, who had previously lived in the United States, who manifested with progressive cerebellar signs and mental deterioration. Clinically she had significant elevations in serum antibodies to the Lyme spirochete. She eventually died and at autopsy was found to have multifocal inflammatory changes in the cerebral cortex, thalamus, superior colliculus, dentate nucleus, inferior olivary nucleus, and spinal cord. Use of Warthin-Starry stain revealed organisms consistent with the appearance of *B. burgdorferi*. Occlusive vasculopathy as well as lymphocytic infiltration of the meninges were found. The pathology in many ways mimics that seen in CNS infection with *Treponema pallidum*.

The syphilis spirochete is often associated with vasculitis, and oblitative endarteritis is typically seen in patients with meningovascular syphilis. The report by Oksi et al. (71) demonstrates the potential for *B. burgdorferi* generating cerebral vasculitis. Oksi et al. described three patients with known Lyme borreliosis who developed intracranial aneurysms. One of the three patients had a brain biopsy that demonstrated lymphocytic vasculitis and perivasculitis. This patient and one of the other two developed a subarachnoid hemorrhage. This is the first case report of cerebral artery aneurysm associated subarachnoid hemorrhage secondary to Lyme borreliosis; Lyme-associated coronary artery aneurysm was previously described in two patients with long-standing borreliosis. Although tissue was not available to establish a causal relationship in the other two patients, the propensity for this organism to invade vascular endothelial cells is known, and thus the association between Lyme disease and aneurysms merits serious causal consideration in clinical scenarios in which both conditions coexist.

**Treatment**

The treatment of Lyme borreliosis depends on the stage of the disease and presence or absence of CNS
infection. Oral doxycycline and amoxicillin are both effective, and a total of 10 days to 2 weeks of therapy is likely to be sufficient in patients with early manifestations such as an ECM rash. Amoxicillin is the preferred antibiotic in children and pregnant or lactating women. Cefuroxime axetil should be given to those in whom doxycycline is contraindicated or who are penicillin allergic. The macrolide antibiotics erythromycin or azithromycin can be substituted but have been found to be less effective (73–75). In a large, randomized, double-blind trial in patients with erythema migrans, amoxicillin was found to be superior to azithromycin in establishing a cure with a lower rate of relapse 6 months after treatment was initiated. Longer courses are necessary for those with arthritic manifestations. Patients who have objective neurologic involvement, with the possible exception of facial palsy, are recommended to have parenteral antibiotics and a longer duration of therapy. Ceftriaxone 2 g/day intravenously for approximately 4 weeks is a standard regimen. Patients with facial palsy and an abnormal CSF should also probably be treated intravenously. Thus, patients with Lyme facial palsy should undergo lumbar puncture to determine whether CSF antibody is present to determine route of administration. There is a recent report by Dotevall and Hagberg (76), however, that challenges the requirement for intravenous therapy in patients with neurologic manifestations. They treated 29 patients with Lyme infection and facial palsy and meningitis with oral doxycycline at a daily dose ranging between 200 and 400 mg for 9 to 17 days. Ninety percent of patients recovered without sequelae at 6 months. Post-treatment CSF evaluation disclosed a marked decrease in inflammatory cells and protein concentrations compared with pretreatment levels. This outcome compares favorably with published studies using intravenous antibiotics for Lyme-associated meningitis and facial palsy. Thus, it is conceivable that patients with milder CNS involvement may be adequately treated as outpatients with oral antibiotics. A prospective randomized trial would be helpful in deciding the most appropriate route of administration. At present there are no published guidelines for therapy of purely ocular manifestations. This is likely partly due to the low frequency in total number of cases of ocular involvement. However, the authors recommend intravenous therapy for 4 weeks for sight-threatening manifestations such as optic neuropathy and oral antibiotics for 2 weeks for anterior segment nonsight threatening conditions.

Prophylaxis

Prevention of Lyme infection can be approached in various ways including tick eradication, protection against tick exposure, antibiotic prophylaxis post-tick bite, or vaccination. Individuals who travel or go hiking in wooded tick-infested regions should wear long trousers tucked into socks with periodic checking for ticks. Post-tick bite antibiotic prophylaxis has not always been found to be useful for prevention of infection. The tick may not belong to the Ixodid genus, prolonged exposure is necessary for infection to occur, and not all Ixodid ticks harbor the spirochete. Even in areas of high Lyme disease prevalence, the percentage of ticks infected may only be one in three. A study in the Lyme, CT, area determined that the overall risk of Lyme disease in placebo-treated patients was only 1.2% (77). The sum of the results of published studies regarding antibiotic prophylaxis is equivocal. Patient anxiety about Lyme disease undoubtedly plays a role in compelling the physician to initiate antibiotic prophylaxis. Thus with the published uncertainty, the decision for such treatment will depend on multiple factors, some of which are unrelated to the pathogenesis of infection. Indeed, current physicians practice the lack of uniformity with respect to antibiotic prophylaxis.

Since reinfection does not occur in patients with an expanded immune response against Borrelia antigens, a vaccine that can potentially confer long-term immunity against Lyme disease is possible. In particular, outer surface protein A (OspA) antigens have been found to be highly immunogenic. A recombinant single protein OspA preparation was thus developed. This vaccine preparation was shown to confer protective immunity against B. burgdorferi in multiple animal trials involving mice and dogs. The mechanism of action is prevention of transfer of spirochete from tick to host via antibody-mediated killing of the spirochete in the tick midgut. Such success subsequently led to safety trials in humans and finally to a multicenter, double-blinded, placebo-controlled study initiated in 1994. This study compared a 30 μg dose of the recombinant vaccine against a placebo vaccine. A total of 10,306 volunteers, ages 18 to 92 years, enrolled in this study involving 14 centers in the United States. The results indicate that the vaccine effectively confers protection up to 20 months after the first injection; however, a third dose is necessary to boost antibody levels and achieve a protection rate of greater than 80% (78,79). A trial investigating the efficacy in the pediatric population is underway. Although the vaccine appears to be efficacious, long-term immunity is unclear. Since antibody levels diminish fairly rapidly and protection is conferred by extent of antibody titers, it is logical that booster shots will be necessary periodically. Despite the early positive published results, a number of questions have yet to be answered. Cost-effectiveness is certainly a paramount issue. The facts are Lyme disease is not lethal, all stages of infection respond to antibiotics, and early disease such as erythema migrans can be effectively treated at a cost of $15 per patient. Moreover, the vaccine would make breakthrough infection or seroconversion difficult to determine, and Western blot analysis of other antigens would need to be performed. The false-positive rate will undoubtedly increase in this scenario. Finally, the full safety profile including the risk in pregnant women and those with immunologic disorders or higher risk HLA antigens was not evaluated and remains to be determined. For example, individuals who have the HLA-DR4 haplotype are at higher risk for development of chronic Lyme arthritis. This antigen preparation in an HLA-DR4 positive individual may in fact stimulate an antibody response that by molecular
Acknowledgment: Supported in part by an unrestricted grant form Research to Prevent Blindness, Inc.

REFERENCES


Author Index

Abdulla, N.
—Eustace, P.: A Case of Ocular Neuromyotonia With Tonic Pupil, 125

Abel, L. A. See Mulhall, L. E.

Aldama, A. E. See Lee, A. G.

Alloni, R. See Verzino, M.

Appel, S. H. See Lee, A. G.

Arsene, S. See Bouvier-Bareil, F.

Averbuch-Heller, L.
—Dell'Ossio, L. F.; Jacobs, J. B.; Rentier, B. F.: Latent and Congenital Nystagmus in Down Syndrome, 166

Avet, P. P.
—Kline, L. B.; Sillers, M. I.: Endoscopic Sinus Surgery in the Management of Mucormycosis, 56

Balcer, L. J.

Barr, D. B.
See McFadzean, R. M.

Barr, D.

Barton, J. J. S.
—Cox, T. A.; Digre, K. B.: Acquired Convergence-Evoked Pendular Nystagmus in Multiple Sclerosis, 34

Bhatti, M. T.
—Newman, N. J.: A Multiple Sclerosis-Like Illness in a Man Harborizing the mtDNA 14484 Mutation, 28

Bolger, C.
—Hershey, B.: Ocular Microtremor in Oculomotor Palsy, 42

Bolger, C.

Borruat, F.-X.
—Jaques, B.; Durig, J.: Transient Vertical Diplopia and Silent Sinus Disorder, 173

Bosley, T. M.
See Suleh, M. a.

Bouvier-Bareil, F.

Carlow, T. J.
The History of NANOS, 219

Cassidy, L. M. See Good, C. D.

Chen, W.-H. See Kao, Y.-F.

Chou, M.-S. See Kao, Y.-F.

Coulley, D. See Bolger, C.

Cordon, B. C. See McFadzean, R. M.

Dell'Ossio, L. F. See Averbuch-Heller, L.

Dinapoli, L. F. See Averbuch-Heller, L.

Dix, J. See Sorin, M.

Donahue, S. P. See Khoury, J. M.

Dutton, G. N. See Diaper, C. J. M.

Feldon, S. E. See Wang, M. Y.

Frohman, M.
—Luna, P.: 1999 Annual Update of Systemic Disease: Emerging and Re-emerging Infections (Part I), 263

Galetta, S. L.
See Balcer, L. J.
See Gray, L. G.
See Lee, A. G.

Gans, M. S. See Wein, F. B.

Girkin, C. A.
—Perry, J. D.; Miller, N. R.: Visual Environmental Rotation: A Novel Disorder of Visiospatial Integration, 13

Good, C. D.
—Cassidy, L. M.; Moseley, I. F.; Sanders, M. D.: Posterior Optic Nerve Infarction After Lower Lid Blepharoplasty, 176

Gray, L. G.
—Galetta, S. L.; Hershey, B.; Winkelmann, A. C.; Wilt, A.: Inferior Division Third Nerve Paresis From an Orbital Dural Arteriovenous Malformation, 46

Groscurth, P. See Keller, H. B.

Harper, R. L. See Lee, A. G.

Heron, G. See Diaper, C. J. M.

Hershey, B. See Gray, L. G.

Hommet, C. See Bouvier-Bareil, F.

Horgan, M. C.

Hoyt, W. F. See Jones, M. R.

Inukai, G. See Oono, S.

Ishikawa, S. See Yoshitomi, T.

Jacobs, J. B. See Averbuch-Heller, L.

Jaques, B. See Bonani, F.-X.

Job, O. M.
—Schulte, N. J.; Glaser, J. S.: Ocular Microtremor in Oculomotor Palsy, 42

Johnson, L. N. See Lehman, N. L.

Jones, M. R.
<table>
<thead>
<tr>
<th>Author</th>
<th>See</th>
<th>Author</th>
<th>See</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waggoner, R.</td>
<td>Jones, M. R.</td>
<td>Wang, M. Y.</td>
<td></td>
</tr>
<tr>
<td>Sadun, F.; Levin, L. B.; LaBree, L.; Feldon, S. E.: Occurrence of Familial Nonarteritic Anterior Ischemic Optic Neuropathy in a Case Series, 144</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warren, R. W.</td>
<td>Lee, A. G.</td>
<td>Wein, F. B.</td>
<td></td>
</tr>
<tr>
<td>Gans, M. S.: The Perils of a Sneeze, 128</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams, I. M.</td>
<td>Mulhall, L. E.</td>
<td>Winkelman, A. C.</td>
<td>Gray, L. G.</td>
</tr>
<tr>
<td>Wulc, A.</td>
<td>Gray, L. G.</td>
<td>Yoshitomi, T.</td>
<td></td>
</tr>
<tr>
<td>Zambarakji, H.</td>
<td>Newsom, R. S. B.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dural fistula
  arteriovenous, of marginal sinus (abstract), 117
  cavernous, embolization of (abstract), 116
Dural sinus thrombosis, endovascular thrombolytic therapy for
  (abstract), 117
Erblichiosis, visual system effects of, 263
Embolization, of dural cavernous fistulas (abstract), 116
Endovascular stents, for dissecting aneurysm of cervicocranial
  arteries (abstract), 117
Endovascular treatment
  of ophthalmic segment aneurysms (abstract), 116
  thrombolytic, for dural sinus thrombosis (abstract), 117
Environmental rotation, with vestibulopertionetal shunt, 13
Epileptic transmission, in ocular neuro-ophthalmology with tonic pupil, 125
Exophthalmas, third nerve palsies and, 46
Extrastriate quadrantamopha, cerebral polyopia with, 1
Eye disease
  22-kDa antigen in, 71
  thyroid, 54
Eye movements, after head injury, 160
Eyelid retraction, in thyroid ophthalmopathy, 122
Facial bones, adenosquamous carcinoma of (abstract), 113
Facial palsy, peripheral, in cat-scratch disease, 240
Familial nonarteritic anterior ischemic optic neuropathy, occurrence
  of, 144
Fatigue, ptosis in, 257
Facial palsy, peripheral, in cat-scratch disease, 240
Facial bones, adenosquamous carcinoma of (abstract), 113
Fatigue, ptosis in, 257
Fibromuscular dysplasia, dissecting aneurysm of cervicocranial
  arteries in (abstract), 117
Filling-in, perceptual, 84
Functional magnetic resonance imaging, in visual system, 186
Gaze palsy, reversible, disseminated histoplasmosis in, 140
Geniculate nucleus metastasis, 17
Giant cell arteritis, 17, 207
Horner syndrome due to (abstract), 260
Glaucoma, perimetry for, 100
Globe tenting, in head trauma (abstract), 112
Hemifacial spasm
  botulinum toxin A injections for, 7
  neurointerventional diagnosis of (abstract), 116
Hemianopsia, in dissection of internal carotid artery, 156
Hemifacial spasm
  botulinum toxin A injections for, 7
  neurointerventional diagnosis of (abstract), 116
Hemianopsia, in dissection of internal carotid artery, 156
Hemifacial spasm
  botulinum toxin A injections for, 7
  neurointerventional diagnosis of (abstract), 116
High altitude retinopathy, 205
Histocytosis, Langerhans cell, visual loss with, 49
Histopathology, optic nerve, 182
Histoplasma capsulatum, in reversible gaze palsy and optic
  neuropathy, 140
Histoplasmosis, disseminated, in reversible gaze palsy and optic
  neuropathy, 140
Humorous hemianopsia
  as initial manifestation of multiple sclerosis (abstract), 39
  in pediatric patients, 17
Horner syndrome
due to giant cell arteritis (abstract), 260
without arthriosis, traumatic, 148
Human immunodeficiency virus infection
  bilateral ophthalmic nerve palsy with cryptococcal meningitis in, 118
  visual loss with, 207
Humphrey field analyzer, in perimetry, 89
Hydrocephalus, ventriculoperitoneal shunt for, 13
Hydroxyapatite orbital floor prosthesis, CT-generated porous
  (abstract), 113
Infections, emerging and re-emerging, 263
Intracranial infections, fast fluid-attenuated inversion-recovery MR
  of (abstract), 114
Intracranial vascular stenosis/occlusion, magnetic resonance
  angiography of (abstract), 116
Ischemic optic neuropathy
  arteritis, magnetic resonance imaging in, 235
Langerhans cell histiocytosis, visual loss with, 49
Lateral geniculate hemorrhage, traumatic, 207
Leber’s hereditary optic neuropathy, 17, 207
Leukocyte nuclear DNA mutation, 28
Orbital magnetic resonance imaging in, 238
Perimetry for, 89
Letters to editor, 120, 217
Literature abstracts, 112, 260
European, 39
Lyme disease, visual system effects of, 263
Lymphatic capillaries, in meninges of human optic nerve, 222
Lymphoma, central nervous system, MR appearance of (abstract), 114
Macleod neuroretinopathy, acute, 17
Macular star, in neovascularization, 201
Maffucci’s syndrome, neuro-ophthalmologic manifestations of, 62
Magnetic resonance angiography
  for intracranial vascular stenosis and occlusion (abstract), 116
  of neck aneurysm models (abstract), 115
Magnetic resonance imaging
  of activated areas of visual cortex (abstract), 112
  in different visual system evaluation, 17
  for aneurysms of cavernous sinuses, 249
  in arteritic ischemic optic neuropathy, 235
  changes in calcarine area with retinal degeneration (abstract), 112
  in Coats disease (abstract), 112
  for cyclospia (abstract), 112
  fast fluid-attenuated inversion-recovery (abstract), 114
  functional, in visual system, 186
  of head and neck neoplasms (abstract), 113
  for Langerhans cell histiocytosis, 49
  in Leber’s hereditary optic neuropathy, 238
  in multiple sclerosis with various disability levels (abstract), 115
  of primary lymphoma of central nervous system (abstract), 114
  of equivocal cell carcinoma (abstract), 113
  with visual field deficits (abstract), 113
Magnetic resonance pulse sequences, in multiple sclerosis (abstract), 114
Magnetization transfer imaging
  in multiple sclerosis (abstract), 115
  single-dose gadolinium versus triple-dose gadolinium (abstract), 115
Marginal sinus, dural arteriovenous fistulas (abstract), 117
Melanin, botulinum toxin A injections and, 7
Melatonin, in toxic optic neuropathy, 232
Memory-guided saccades, after head injury, 160
Meningeal lymphatic capillaries ed, 222
Meningioma, 207
Meningitis, cryptococcal, bilateral trochlear nerve palsy with, 118

Protein diet, in toxic optic neuropathy, 232
Proton magnetic resonance spectroscopy
in Coats disease (abstract), 112
of squamous cell carcinoma (abstract), 113
Pseudotumor cerebri, clinicopathological correlation of excised
choroidal neovascular membrane in (abstract), 39
Pterygopalatine fossa, heterotopic brain in (abstract), 113
Ptosis
in Horner syndrome, 148
intracranial (atigable, 257)
Pollitt phenomenon, 17, 207
symptoms and management of, 12
Pupil
in anisocoria, 153
perimetry of versus threshold visual perimetry, 89
Quadranthopia, extrastriate, cerebral polyopia with, 1
Radiation therapy, for Langerhans cell histiocytosis, 49
Radionurogery, predicting response to (abstract), 117
Retina
Segmentation of, MR changes in calcarine area with (abstract), 112
22-kDa antigen in disease of, 71
neuro-ophthalmology and, 17, 207
vascular disease and, 207
in visual field defects, 84
Retinal detachment
excudative, 201
serous, 201
Retinopathy
cancer-associated, 207
high altitude, 205
non-cancer-associated, 71
Rhino-orbital mucormycosis, endoscopic sinus surgery for, 56
Rhino-orbito-cerebral mucormycosis, endoscopic sinus surgery for, 56
Saccades, after head injury, 160
Scleral traction cysts, 207
Sensations, in toxic optic neuropathy, 232
Silent sinus syndrome, transient diplopia and, 173
Sinal disorders, transient diplopia and, 173
Sinal surgery, for mucormycosis, 56
Skeletal enchondromas, multiple, 62
Skull base
adenosquamous carcinoma of (abstract), 113
atypical paragangliomas of (abstract), 113
Sneeze, perils in, 128
Spectroscopy, proton magnetic resonance
in Coats disease (abstract), 112
in squamous cell carcinoma (abstract), 113
Squamous cell carcinoma, proton MR spectroscopy of (abstract), 113
Stents
for dissecting aneurysm of cervico-cranial arteries (abstract), 117
placement of for neurovascular disease (abstract), 116
Stereotactic radiotherapy (abstract), 117
Sturge-Weber syndrome, abnormal ocular enhancement in (abstract), 114
Subarachnoid space, lymphatic capillaries in, 222
Supranuclear extramedullary hematomas (abstract), 17
Surgery, endoscopic sinus, 56
Surgical ligation, for dissecting aneurysm of cervico-cranial arteries (abstract), 112
perimetry of versus threshold visual perimetry, 89
Test-retest analysis, with functional magnetic resonance imaging in (abstract), 112
Terson syndrome, 17
Tamoxifen retinopathy, 207
Tetracaine retinopathy, 207
Third nerve palsy of, with arachnoid cysts of cavernous sinus, 249
tarsus of
hemorrhagic arachnoid cyst with (abstract), 114
in inferior division, 46
Threshold visual perimetry, versus objective pupil perimetry, 89
Thrombolytic therapy, for dural sinus thrombosis (abstract), 117
Thyroid eye disease, early, 54
Thyroid orbitopathy, spontaneous resolution of upper eyelid retraction in, 127
Toxic optic neuropathy, after melatonin, Zoloft, and high-protein diet, 232
Transient vertical diplopia, silent sinus disorders and, 173
Trauma
brain injury in, bedside tests of saccades after, 156
Horner syndrome without anhidrosis in, 148
lateral geniculate hemorrhage with, 207
Trocilic nerve palsy, 252
bilateral, 118
Trolite's phenomenon, 84
Tuberculosis meningitis, 201
Tumor, metastatic to optic tract, 17
22-kDa antigen, in optic nerve and retinal diseases, 71
Vascular anomalies, intracranial, 17
Vascular disease, retina and, 207
Vascular risk factors, in cranial nerve palsy, 252
Vascular stenosis, magnetic resonance angiography of (abstract), 116
Vascular risk factors in cranial nerve palsy, 252
Vascularities, magnetic resonance angiography of (abstract), 116
Ventriculoperitoneal shunt
with choriocapillary atrophy, 100
with low vision, 15
Ventricular enlargement, with intracranial hypertension, 182
Tonic pupil, ocular myoclonia with, 125
Topical optic neuropathy, after melatonin, Zoloft, and high-protein diet, 232
Visual abnormalities, intracranial, 17
Visual field
30-2 versus 24-2, 100
loss of, optic atrophy in, 17
perimetry of, 89
Virtual environmental rotation after, 13
Visuospatial integration, disorders of, 13
Visual allesthesia, 13
Visual cortex
magnetic resonance imaging of activated areas of (abstract), 112
T2 shortening in (abstract), 116
T2 shortening in (abstract), 115
Virtual environmental rotation, 13
Visual pathway, multifocal involvement of in Langerhans cell histiocytosis, 49
Visual system
emerging and re-emerging infections affecting, 263
functional magnetic resonance imaging in, 186
problems of with Pulfrich phenomenon, 12
Wallerian bilateral internuclear ophthalmoplegia, 131
Whipple's disease, visual system effects of, 263
Wills, circle of, 126
Wolffram syndrome, optic atrophy in (abstract), 39
Zoloft, in toxic optic neuropathy, 232