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For J. Lawton Smith

No one is entirely sure just how happy is "a dead hog in the sunshine," but our teacher and colleague Lawton Smith must come close, feet-up in retreat, eating fried chicken and hush puppies in South Carolina. After 30 years at the Bascom Palmer Eye Institute, and various lustrous intervals at Duke, Emory, Johns Hopkins and Mass. Eye & Ear, one of the remarkable figures in ophthalmology has retired from active practice and as Founding Editor of the Journal of Neuro-Ophthalmology. For a third of a century, Lawton Smith has popularized our specialty with a style of "down in the country" solutions to diagnostic dilemmas, and with priceless anecdotes and practical management "pearls" abundantly helpful in "office practice . . . for the men in the trenches." His infectious linguistic technique of "latest gems" and Southern-fried witticisms set the pace for scores of admiring young physicians, and influenced more than one novice (this writer included) to embrace neuro-ophthalmology as a lifelong career.

Author and editor of a series of collections of current-concept essays, and father of the long-running (almost annual since 1963) University of Miami Neuro-Ophthalmology Symposia, Lawton transported the semi-remote discipline of neuro-ophthalmology into the realm of the practical and accessible. For general practitioners and devotees alike, Lawton's inimitable recipe combined erudition, wholesome simplification and unique humor to provide an educational feast. At the December Miami Symposia, Lawton regularly convened an all-star cast, including the likes of Frank Walsh, Dave Cogan, Richard Lindenberg, Bill Hoyt, and numerous other illuminating expert lecturers.

Like Will Rogers, J.L.S. never met a disease he didn't like! To his choreographic animation of internuclear ophthalmoplegia, Lawton added a tongue-clucking soundtrack. His good friend and old comrade Noble David once described Lawton's portrayal of the potential tumorous expansion of pituitary adenomas: "Anyone who has ever seen Dr. Smith in conference at half crouch in his far-from-silent pantomime of the inflamed intrasellar growth, arms and legs aggressively flailing out at the imaginary regional anatomy, will not easily forget the lesson."

While others formed committees, analyzed manuscript rejection rates, and agonized for and against the founding of a journal dedicated to neuro-ophthalmology, Lawton just did it! With an eclectic board of editors, and a sworn policy of "No DKAs" (Doctor Killing Abbreviations), the first issue of JCNO was born in March 1981, published by Masson. And practically every quarterly issue thereafter bore the unmistakable mark of the Editor-in-Chief, complete with an at-home corresponding address in South Miami, until Hurricane Andrew swept away the roof of the "Editorial Offices."

Men like Lawton Smith may retire from medical practice and public authorship, but they do not diminish in stature nor just fade away. J.L.S. will be fondly remembered by the myriad patients to whom he dedicated his medical vocation and life, and by the long line of medical students, residents, fellows, faculty members, and colleagues to whom he gave so much valuable information and with such a singular delight. In admiration and affection, we thank Lawton Smith for his incalculable contributions to our discipline and to this Journal.

Joel S. Glaser, M.D.
for the Board of Editors
Visual Function in Neurofibromatosis

A. Castanheira-Dinis, M.D., Manuela Novais, M.D.,
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Objectives: To evaluate the visual function in patients with neurofibromatosis (NF) and to study the etiology and incidence of visual dysfunction associated with NF.

Patients and Methods: A total of 75 patients with diagnostic criteria for NF were evaluated. Neuro-ophthalmological examination as well as electrophysiological and imaging studies were performed. Special attention was given to the presence of visual dysfunction and to its correlation with the ophthalmic changes that were found.

Results: Ocular findings were present in 42 (56%) patients. Visual dysfunction was identified in only 11 (14.7%) patients. Visual acuity decrease was the most prevalent change, being present in eight (72.7%) of patients with visual dysfunction. Nystagmus, strabismus, visual field defects, and color vision defects were also detected. Therapy is also reviewed. The prognosis of the 11 patients with visual dysfunction was unfavorable, and is discussed.

Conclusion: The prevalence of NF and ophthalmological findings related to it make the problem of visual dysfunction in NF a serious one, deserving of the attention of all ophthalmologists. Clinical examination, associated with complementary diagnostic techniques (mainly imaging studies), allows NF’s identification, definition, and therapy. The high prevalence of asymptomatic ocular findings in NF (73.8%) highlights the role of imaging techniques in its evaluation.

Key Words: Neurofibromatosis—Visual function—Gliomas—MR.

Neurofibromatosis (NF) is a systemic disease transmitted as an autosomal dominant trait (1–3). It is considered the most frequent of the phakomatoses, its gene being present in one in every 3,000–4,000 individuals (1–3). Two types are well known, NF1 and NF2, but other types may exist with different clinical and genetic features. However, existence of subtypes as autonomous entities is still under investigation (1–5). The high incidence and polymorphism of NF explain the many scientific reports on this disease that deal with clinical findings, genetic patterns, diagnosis, and therapeutic approaches.

As it is a disease of neural crest origin, ocular findings are frequent and age-related. In NF1, ocular changes are frequently the first to be noticed, and their identification is accepted as a fundamental criterion for NF classification. Thus, ophthalmologists play a major role in diagnosing and defining this disease; it is, therefore, natural to find a large number of reports concerning NF in the ophthalmic literature.

Although ophthalmologists always evaluate visual function in NF patients and prescribe the most appropriate measures for correction of any anomalies found, results of such work are not usually published or appear only as complementary data. The study of visual function in NF patients, most of whom are children, incidence of related systemic disturbances, incidence of visual dysfunction, characterization of its etiology, efficacy of therapeutic measures, and visual prognosis constitute the basis of the present study.

PATIENTS AND METHODS

From January 1990 to December 1994 (5 years), 78 patients who were considered to have NF were evaluated retrospectively at the Neuro-Ophthalmology and Pediatric Ophthalmology Depart-
ments of the Santa Maria Hospital Eye Clinic. Of these 78, three patients were excluded from the study, including a 53-year-old man with criteria for NF1 and bilateral diabetic maculopathy; a 33-year-old man with criteria for NF1, a left eye (grade C) proliferative vitreoretinopathy after retinal detachment; and a 12-year-old boy with criteria for NF1 and a disfiguring, posttraumatic, left eye corneal opacity. Of the remaining 75 patients, 72 (96%) fulfilled the National Institutes of Health Consensus Development Conference (6) for NF1, two were probably NF2, and one was likely to have an NF5. Data concerning those patients are shown in Table I. Most (72%) were children and sex distribution did not show significant differences.

Whenever possible, patients were submitted to a full neuro-ophthalmological examination, electrophysiological studies, and radioimaging. Neuro-ophthalmological examination was adapted to patient age and, whenever possible, included visual acuity assessment, evaluation of eye movements and pupillary reflexes, anterior segment biomicroscopy, posterior segment examination with direct ophthalmoscopy, indirect ophthalmoscopy or 90 D lens, color vision assessment with Farnsworth 15 and/or 100 Hue tests, and visual field evaluation by kinetic perimetry using a Goldmann perimeter. For adults and verbal children, visual acuity was evaluated using a Snellen chart at 6 m, but for preverbal children, preferential looking and STYCAR were the selected examination techniques. Preferential looking was assessed using Teller acuity cards and standard procedures.

STYCAR stands for sheridan tests for young children and retarded are used to assess visual competence during infancy and early childhood, and in handicapped children. STYCAR includes several tests (single-letter cards, miniature toy test, graded balls tests, rolling ball test, mounted balls test, Snellen equivalents, and others), each one being specially adapted to a certain age group and to different levels of handicap. They are used only when an appropriate result cannot be obtained with preferential looking tests. In our patients, STYCAR was used for only two children (case 3, a 3-year-old girl, and case 9, a 7-year-old girl).

TABLE I. Population (n = 75)

<table>
<thead>
<tr>
<th></th>
<th>14.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
</tr>
<tr>
<td>Adults (&gt;18 yr)</td>
<td>21</td>
</tr>
<tr>
<td>Mean age (ys)</td>
<td>33.7</td>
</tr>
<tr>
<td>Children (=16 yr)</td>
<td>64</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>6.5</td>
</tr>
</tbody>
</table>

In case 3, the mounted balls test was used. In this test, six plastic balls of 6.3, 5.1, 3.8, 3.5, 1.9, and 1.3 cm diameter are used. The child faces a 71.3 x 60.96 cm screen placed at 3 m, and the examiner holds a ball completely still in a position a few inches beyond the edge of the screen for 2-3 s. Then, the ball is rapidly removed from the child's sight behind the screen, being presented again for 2-3 s at the same distance from the opposite edge of the screen. In response, the child should swiftly move his eyes to fixate the ball in the new position. The balls are presented in order of decreasing size and results are registered. Visual acuity is determined as follows: ball of 6.3 cm, 6/18; ball of 5.1 cm, 6/36; ball of 3.8 cm, 6/24; ball of 3.5 cm, 6/18; ball of 1.9, 6/12; and ball of 1.3 cm, 6/9. Smaller balls may be used: ball of .96 cm, 6/6; ball of .62 cm, 6/4.5; ball of .47 cm, 6/3; and ball of .32 cm, 6/2.5.

In case 9, single-letter cards were used. In this test, cards are presented at 3 m and the child tries to match the letters pointed by the examiner with those displayed in a key-card. Visual acuity is determined as follows: O, 6/60; X, 6/36; V, 6/24; AT, 6/18; UX, 6/12; HT, 6/9; OX, 6/6; TV, 6/4.5; and HO, 6/3.

In each age group, visual acuity was evaluated considering preferential looking normal values as a reference: neonate, 20/800; 1 month, 20/400-20/200; 3-4 months, 20/200-20/100; 9-12 months, 20/100-20/50; 18 months, 20/50-20/25; 24 months, 20/25; and 36 months, 20/20. Although these guidelines are useful to define normal and decreased visual acuity, careful interpretation was attempted in every case.

Visual evoked potentials (VEPs) were performed with "BioSistemas Studio" equipment and an Olivetti computer. Each record was made by summarizing responses to 128 stimuli, presented at a frequency of 1.6 Hz under monocular viewing conditions. The patient was seated 125 cm in front of a square grating and fixated a 1-cm diameter red target. A pattern stimulus was generated by a video monitor with a spatial frequency of 30' arc, 100% contrast, and acquisition time of 512 ms. Not only was the general morphology of the recording analyzed, but amplitude and latency of the P100 wave were quantified.

VEP recording was attempted on every patient. Pattern stimuli were used when visual acuity was >1/10 and patient age was ≤4 years old. Flash stimuli were preferred when these conditions were not present.

Electroretinography (ERG) was performed with "BioSistemas Studio" equipment and an Olivetti computer whenever there were retinal lesions.
Flash ERGs were obtained with bilateral mydriasis after 1% tropicamide. Photopic ERGs were recorded with the retina adapted to an ambient light intensity of ~300 lux. Scotopic ERGs were recorded in a completely dark room with an analysis time of 128 ms. A complete study of each recording was carried out with photopic and scotopic retinal adaptation. Oscillatory potentials, amplitude (mv), and latency (ms) of scotopic b-waves were all evaluated.

Imaging studies—computed tomography (CT) and/or magnetic resonance (MR)—were also performed in all cases.

When NF2 was diagnosed, an audiogram was requested.

Special attention was paid in evaluation of visual acuity to identification of other forms of visual dysfunction and correlation to ocular changes that were found.

RESULTS

Results are shown in Tables 2 and 3.

NF associated ocular changes were present in 42 (56%) of the 75 patients (Table 2). Although 33 patients had only one type of abnormal ocular finding, two different ocular manifestations were found in nine patients.

One must emphasize that in this group of 42 cases, 31 (73.8%) patients did not show any evidence of visual dysfunction. Of these 42 patients, 16 were adults and 26 were children; thus, 76.2% of the adults presented ocular findings while only 48.1% of the children had ocular abnormalities.

Lisch nodules were the ocular finding most frequently found (42.3%). It seems of interest to mention their appearance in a 3-year-old child. Optic pathway gliomas were found in 10 (13.3%) cases and retinal hamartomas in two cases. Three children had lens opacities and two of these had diagnostic criteria for NF1. Sphenoid dysplasia or hypoplasia was present in three patients. One of these patients had a pulsatile proptosis in association with an orbital encephalocele and absence of the greater wing of the sphenoid.

Eleven patients had NF ocular changes associated with visual dysfunction (Table 3). Of these 11 patients, seven had more than one recognizable form of visual dysfunction and only in two cases (cases 4 and 10) was that dysfunction unilateral. Table 4 shows, in detail, the ophthalmological manifestations found in these 11 patients as well as results of the different diagnostic tests performed and the different therapeutic options considered.

Among the various forms of visual dysfunction that were recognized, decreased visual acuity was the most prevalent [(72.7%) eight patients] affecting both eyes in six cases. Of these eight patients, six had optic pathway gliomas as a direct cause of that disturbance. In case 5, an 8-month-old child, a precise evaluation of visual acuity was not possible, but the presence of nystagmus, and optic nerve chiasmal and optic tract glioma supported the presence of a visual acuity impairment. In case 4, the association of a combined pigment epithelial and retinal hamartoma affecting the macular region definitely contributed to the visual acuity decrease. In the remaining cases, a retinal hamartoma and cataract (case 8) and congenital glaucoma (case 11) were the probable causes for this type of visual dysfunction.

Nystagmus was found in three (cases 1, 2, and 5) patients and strabismus was present in two (cases 3 and 4) patients. The etiology of these findings is, probably, secondary to the visual acuity decreases that, in these five patients, was due to the presence of optic pathway gliomas.

Four patients (cases 1, 2, 6, and 7) had visual field defects. All of these had chiasmal gliomas, and a precise correlation between tumor location and morphology of the visual field defects was found.

Five patients (cases 1, 2, 7, 8, and 10) also had color vision defects.

Electrophysiological studies, CT, and MR were performed whenever possible, confirming and completing the clinical findings.

Therapeutic approaches are shown in Table 4, and included periodic surveillance, refractive correction, trabeculectomy for congenital glaucoma in case 11, ventriculo-peritoneal cerebrospinal fluid (CSF) shunting in case 9 for hydrocephalus control and chiasmal glioma radiotherapy in cases 6 and 7. As expected, visual function recovery was not possible in many cases [eight (72.7%) patients] given the presence of optic nerve atrophy or severe macular lesions.

Table 5 shows the systemic findings in these 11 patients and includes relevant data concerning their families.

<p>| TABLE 2. Ocular/orbital findings (42 patients) |</p>
<table>
<thead>
<tr>
<th>Finding</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisch nodules</td>
<td>32 (42.3)</td>
</tr>
<tr>
<td>Optic pathway gliomas</td>
<td>10 (13.3)</td>
</tr>
<tr>
<td>Lens opacities</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Retinal hamartomas</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Sphenoid dysplasia</td>
<td>3 (4.0)</td>
</tr>
<tr>
<td>Congenital glaucoma</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>
TABLE 3. Visual dysfunction (11 patients)

<table>
<thead>
<tr>
<th>Visual acuity decrease</th>
<th>Nystagmus</th>
<th>Strabismus</th>
<th>Visual fields defects</th>
<th>Color vision defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Case 2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Case 3</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Case 4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Case 5</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Case 6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case 7</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case 8</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case 9</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case 10</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Case 11</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Cafe-au-lait spots were present in 63.6% of cases. Cutaneous neurofibromas occurred in 18.2% of patients.

In case 4, which is a very interesting since the patient had no diagnostic criteria for either of the two types of NF, there were cutaneous plexiform schwannomas. Here, the diagnostic hypotheses of schwannomatosis, a new type of NF, or an incomplete form of NF2 were all considered. This clinical case was presented as a poster during the European Congress on Paediatric Ophthalmology and Orthoptics in Maastricht, October 1994.

Association with other central nervous system (CNS) changes occurred in 72.7% of patients. Although most of these were asymptomatic and needed no surgical treatment, in case 4, a large left hypoglossal nerve schwannoma, causing tongue hemiatrophy with fasciculations, was scheduled for surgical excision. In case 9, ataxia was the result of the presence of pontine and cerebellar hamartomas; obstruction of the foramen of Monro caused hydrocephalus requiring ventriculo-peritoneal CSF shunting.

Bony abnormalities were present in two of the three cases of sphenoid dysplasia or hypoplasia already mentioned.

Table 5 also shows the incidence of NF in these patients' relatives (45.4%). It was common to find more than one relative affected. The patients of cases 6 and 7 are sisters. A positive family history was found in 50 of the 75 (66.7%) patients reported here.

DISCUSSION

Ocular changes were found in 42 of 75 (56%) patients. Although most of these 75 patients were children (72%), the incidence of these ocular findings was greater among the adults (76.2%) than children (48.1%). This is not surprising considering the age-related expression of NF.

Although ocular changes in NF were frequent, visual dysfunction was present in only 14.7% of patients. Probably, the re-evaluation of those 14 patients who did not return for follow-up would lead to detection of more cases of visual dysfunction. The absence of reports on this subject makes comparison with other studies impossible, but, in our opinion, we find this low incidence easy to explain, since, in most cases, Lisch nodules were the only ocular finding and they do not cause visual dysfunction. We found Lisch nodules in 42.3% of patients while most authors report values of 75-95% (1,2,7,8). Since Lisch nodules become more frequent with age, this low incidence probably results from the young age of most of the children included in this group (mean age of 6.5 years).

Optic pathway gliomas, as opposed to Lisch nodules, were almost always associated with visual dysfunction and were the main cause in the present study. Of the 10 patients with glioma, 75 cases, nine (90.0%) were symptomatic. This incidence of optic glioma in NF, 13.3%, is almost identical to those reported by most authors, ~15% (1,2,9-11).

NF-associated optic pathway gliomas have a better prognosis than do isolated optic gliomas, so clinical surveillance was a common option in these 10 patients (1,9). Radiotherapy was performed when the chiasm was involved and tumor growth was confirmed by clinical evaluation and imaging. Results were good, with tumor mass regression and clinical improvement without significant complications after 1 year of clinical follow-up. Optic pathway glioma therapy is still controversial. Often the best option is surveillance, but, when growth is evident or a clinical deterioration occurs, therapy is mandatory and may consist of surgical excision, radiotherapy, or chemotherapy. In chiasmal gliomas, the rate of complications associated with surgery is high, so that radiotherapy is preferred or, according to some authors, chemotherapy. Age is a crucial factor in the therapeutic decision (9,12-14). The presence of hypothalamic glioma in case 6 was also an important factor in choosing radiotherapy. In case 9, CSF ventriculo-peritoneal shunting was required for hydrocephalus.

### TABLE 4. Ocular findings, diagnosis and treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Type</th>
<th>Ocular finding</th>
<th>Complementary diagnostic procedures</th>
<th>Imaging</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>16 yr</td>
<td>1</td>
<td>VOD = 20/70; VOS = 20/50 (astigmatism)</td>
<td>VEP p, abn. conduction OD; OS VF, bitemporal hemianopia F100: R/G</td>
<td>MR</td>
<td>Refraction Follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulsatile proptosis Horizontal nystagmus ODP pallor Chiasmal glioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>18 yr</td>
<td>1</td>
<td>VOD = 20/50; VOS = 20/200 (high myopia)</td>
<td>YEP f, abn. conduction OD VF, bitemporal hemianopia F100 OD; OS; R/G: B/Y</td>
<td>MR</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Horizontal nystagmus Lisch nodules Cortical lens opacities ODP pallor, myopic crescent CD ON and chiasmal glioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>3 yr</td>
<td>1?</td>
<td>Stycar: OD = 20/30 OS = 20/30</td>
<td>VEP f, abn. conduction OD</td>
<td>RM</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strabismus CD ON glioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>4 yr</td>
<td>2?</td>
<td>VOD – Fingers at 1 m; VOS = 20/20</td>
<td>VEP f, abn. conduction OD</td>
<td>CT</td>
<td>Schwannoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strabismus</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RPE hamartoma</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CD ON glioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>6 mo</td>
<td>1</td>
<td>Follows objects Nystagmus CD papilledema; OS ODP pallor OLT, chiasma and optic tract glioma</td>
<td>VEP p, abn. conduction OD; OSVF, bitemporal hemianopia</td>
<td>CT</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F100, N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>15 yr</td>
<td>1</td>
<td>VOD = 20/20, VOS = 20/25 (myopic)</td>
<td>VEP p, abn. conduction OD; OSVF, bitemporal hemianopia</td>
<td>CT</td>
<td>Refraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ODP pallor, myopic retinal changes</td>
<td></td>
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<td></td>
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<td>ON and chiasma glioma</td>
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<tr>
<td>7</td>
<td>F</td>
<td>17 yr</td>
<td>1</td>
<td>VOD = 20/20 VOS = 20/20</td>
<td>VEP p, abn. conduction ODVF, left homonymous hemianopia</td>
<td>CT</td>
<td>Radiotherapy</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Lisch nodules Flight hemichiasma and right optic tract glioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>11 yr</td>
<td>1?</td>
<td>VOD = 20/40; VOS = 20/70 (amblyopia OS, anastometropia)</td>
<td>VEP p, abn. conduction OSVF, NF100: R/G OS</td>
<td>MR</td>
<td>Refraction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lisch nodules OS lens opacities Macular lesion OS (hamartoma?)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>7 yr</td>
<td>1</td>
<td>Stycar: RE = 20/20? LE: 20/20 (searching VF); Myopia</td>
<td>Not cooperative for AV (Snellen); VEP, VF</td>
<td>CT</td>
<td>VPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lisch nodules ODP pallor (+ OD) OD infranuclear ON and chiasma glioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>50 yr</td>
<td>1</td>
<td>VOD = 20/20 VOS = 20/20 POAG OD, OS OD ON glioma</td>
<td>VF, N: AP; OD f blind spot, superior nasal step</td>
<td>CT</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VEP p; abn. conduction OD F100: R/G OD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>4 yr</td>
<td>1</td>
<td>VOD: 20/200; VOS: 20/40 (astigmatism)</td>
<td>VEP p; abn. conduction OD; OS ERG: subnormal</td>
<td>CT</td>
<td>Trabeculectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CD ODP: abnormal capping OD congenital glaucoma (buphthalmos)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abn, abnormal; AP, automated perimetry; B/Y, blue/yellow; ENT, ears, nose, and throat; F, female; M, male; N, normal; OD, optic disc; ON, optic nerve; POAG, primary open angle glaucoma; R/G, red/green; RPE, retinal pigment epithelium; VEP, visual evoked potentials (p, pattern; f, flash); VF, visual fields; VOS, visual acuity left eye; VPS, ventriculo-peritoneal shunting; VOD, visual acuity right eye.

Lisch control. Identical approaches have been recommended by other authors (14,15).

Retinal hamartomas were present in the two cases of probable NF2, which is in accordance with the greater incidence of these lesions in that type of NF (16-18).

Lens opacities are described only in NF2, in which they may occur in >75% of the cases (19-21). Among these 75 patients, there was one child with lens opacities and poorly defined diagnostic criteria for NF. This child, reported as case 8, had Lisch nodules, a retinal hamartoma, cafe-au-lait spots, and deep brain gliomas. It is our experience that, in some cases, full expression of NF occurs later, making classification difficult or even impossible at any given moment. In case 2, diagnostic
TABLE 5. Systemic findings and family history

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Type</th>
<th>Cutaneous findings</th>
<th>CNS findings</th>
<th>Bony findings</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>16 yr</td>
<td>1</td>
<td>Cafe-au-lait spots</td>
<td>Temporal arachnoidal cyst</td>
<td>Right sph greater wing</td>
<td>Sister, mother, and grandmother (maternal), NF1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>18 yr</td>
<td>1</td>
<td>Cafe-au-lait spots, Neurofibromas</td>
<td>Encephalic hamartomas</td>
<td>Dysplasia, Orbital deformation and facial asymmetry</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>3 yr</td>
<td>1?</td>
<td>Cafe-au-lait spots</td>
<td>Brain stem glioma infiltration</td>
<td></td>
<td>Sister, mother, and aunt (maternal), NF1</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>4 yr</td>
<td>2?</td>
<td>Plexiform schwannomas</td>
<td>Left hypoglossal schwannoma, Right foramen magnus tumor</td>
<td></td>
<td>Grandmother (paternal) with identical tumor</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>18 mo</td>
<td>1</td>
<td>Cafe-au-lait spots</td>
<td>Hypothalamic glioma</td>
<td></td>
<td>Daughter, cafe-au-lait spots</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>15 yr</td>
<td>1</td>
<td>Cafe-au-lait spots</td>
<td>Left deep temporal glioma</td>
<td></td>
<td>Mother, NF1</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>17 yr</td>
<td>1</td>
<td>Cafe-au-lait spots</td>
<td>Left Rolandic hamartoma or glioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>11 yr</td>
<td>1?</td>
<td>Cafe-au-lait spots</td>
<td>Right hemiparesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>7 yr</td>
<td>2?</td>
<td>Cafe-au-lait spots</td>
<td>Hypothalamic glioma, Mono toramen obstruction (hydrocephalus and VPS), Cerebellum and pons hamartomas (ataxia), Macrocephalus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>50 yr</td>
<td>1</td>
<td>Facial cutaneous neurofibromas</td>
<td></td>
<td>Right sph greater wing hypoplasia</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>4 yr</td>
<td>1</td>
<td>Cafe-au-lait spots</td>
<td></td>
<td></td>
<td>Mother, NF1</td>
</tr>
</tbody>
</table>

CNS, central nervous system; F, female; M, male; Sph, sphenoid; VPS, ventriculo peritoneal shunting.

Criteria for NF1 were present and anterior subcapsular lens opacities were found. This clinical feature, although rare, is described by some authors (2).

The two patients with sphenoid dysplasia or hypoplasia did not have visual dysfunction related to the finding. In case 1 a pulsatile proptosis was present. These bony defects are frequently described in association with NF1 (1,3,22). The third case of sphenoid dysplasia reported here, although not having visual dysfunction, deserves special mention since it represents the classical association, described by Walsh and Hoyt, of absence of the greater wing, orbital encephalocele, and plexiform neurofibroma of the frontal region and superior lid (1).

Visual field defects were found in four patients with chiasmal gliomas. In five patients, children <5 years of age, visual field evaluation was not performed. Kinetic perimetry was performed in every patient aged ≥5 years, although the patient of case 9 did not cooperate with this test.

Color vision defects were present in five patients. Color vision was evaluated in all patients >4 years of age using the Farnsworth 100-Hue (except case 9, who did not cooperate). Red/green defects were, as expected, the most prevalent. In case 2, there was also a blue/yellow defect. Retinal changes related to high myopia are the most probable explanation for that finding.

As shown in Table 5, different ancillary examination techniques were used in order to obtain a better definition of visual dysfunction. VEPs were performed in nine patients and correlated well with the presence of optic gliomas or, in case 11, of optic nerve glaucomatous damage. The patient reported in case 5 abandoned follow-up before a VEP could be done, and the patient in case 9 was not cooperative.

CT and MR were essential for locating and quan-
tifying optic and CNS lesions and in order to arrive at a therapeutic decision.

CONCLUSIONS

Considering the high prevalence of NF in the general population, visual dysfunction in NF has become a significant problem deserving greater attention.

Optic pathway and retinal lesions are usually untreatable and associated with permanent damage. Thus, it is of primary importance that NF patients and their relatives undergo a neuro-ophthalmological examination as soon as the diagnosis of NF is established or suspected in order to widen the therapeutic options, exclude other lesions, improve visual prognosis, or increase survival time.

Ocular changes are easier to detect in adults, in whom they occur more frequently and in whom cooperation is much better, the latter being the reason why ocular findings were more prevalent in the adult group. However, 11 patients had visual dysfunction and, of those, eight (72.7%) were children. A prompt diagnosis is, therefore, mandatory and only feasible through an efficient interdisciplinary approach. Pediatricians should refer all NF patients and their relatives undergo a neuro-ophthalmological examination as soon as the diagnosis of NF is established or suspected in order to widen the therapeutic options, exclude other lesions, improve visual prognosis, or increase survival time.

One must also emphasize the high frequency (73.8%) of asymptomatic ocular findings and highlight the importance of always complementing clinical assessment with other examination techniques, particularly neuroimaging, so that all abnormalities may be recognized.

REFERENCES

"Normal Pressure" Pseudotumor Cerebri

Jeffrey P. Green, M.D., Nancy J. Newman, M.D., Zachary N. Stowe, M.D., and Charles B. Nemeroff, M.D., Ph.D.

We present a case report of a patient with clinical features suggestive of pseudotumor cerebri (PTC), without a documented elevated measurement of intracranial pressure (ICP). Chart review was done of one patient's clinical course over a 28-month period. The patient was treated for PTC even though she never had a documented elevated ICP. Her signs and symptoms, including headache, disc edema, and visual field loss, all showed improvement with standard PTC therapy, which ultimately included optic nerve sheath fenestration (ONSF). Her presenting symptoms of clinical depression were also relieved with this treatment. PTC may present without an elevated ICP as defined by current standards. Some patients may be more susceptible to lower levels of ICP and develop this syndrome, and it may be responsive to standard PTC therapy. Further investigation may warrant that clinical depression be included as another minor symptom of PTC.

Key Words: Pseudotumor cerebri—Optic nerve sheath fenestration—Depression—Intracranial pressure.

Pseudotumor cerebri (PTC) is a syndrome of raised intracranial pressure of unknown etiology. The modified Dandy criteria for the diagnosis of PTC are well known: (a) signs and symptoms of increased intracranial pressure; (b) absence of localized findings on neurologic examination; (c) normal neuroradiologic studies; (d) awake and alert patient; (e) no other cause of increased intracranial pressure present (1). The major symptoms of PTC include headache, transient visual obscurations, blurred vision, pulsatile tinnitus, and diplopia (1,2). Other minor symptoms include parasthesias, back and leg pain, arthralgias, and unsteady gait (3).

Johnston et al. (4) called attention to some cases that bear a close resemblance to PTC but fail to comply with one or more of the accepted diagnostic criteria. These authors proposed that the concept of PTC be broadened to include other atypical forms. One of these atypical forms was that of so-called "normal pressure pseudotumor" syndrome. We report a patient who presented with symptoms of clinical depression and headache and possible "normal pressure pseudotumor cerebri." Her symptoms and signs improved after optic nerve sheath fenestration.

CASE REPORT

An 18-year-old, 66-inch tall, 145-pound woman with a mildly overweight body habitus, was admitted to the general psychiatric and clinical research unit with a history of depression for 15 months and chronic fatigue syndrome for approximately 3 years diagnosed by a local psychiatrist. Her symptoms included complaints of sadness, lack of motivation, hyperpsomnolence (up to 16 h per day), hyperphagia, fatigue, difficulty concentrating, and a history of morbid thoughts. She had been treated for 10 months with fluoxetine
(Prozac) up to 60 mg/day, with only a partial remission of symptoms. The fluoxetine was discontinued and the patient was started on desipramine (Norpramin) up to 100 mg/day, which was discontinued secondary to a rash. Upon admission her medications included lorazepam (Ativan) 1 mg at bedtime, and an oral contraceptive, Ortho Novum 1/35. Her admission Beck Depression Inventory (BDI) (5) was 15, and she was started on sertraline (Zoloft) 50 mg/day. On her admission physical examination the psychiatrist noted that she had bilateral disc edema.

Further questioning revealed that the patient had been experiencing recurrent headaches and eye pain with no complaints of decreased visual acuity or visual field loss. She denied transient visual obscurations or diplopia. She also denied the use of vitamin A, steroids, or tetracycline. On examination her vision was 20/20 in both eyes. Pupils were normal. Intraocular pressure was 16 in both eyes, and motility and slit lamp examinations were unremarkable. Fundus examination revealed bilateral disc elevation (Fig. 1), with blurred margins and mild hyperemia in both eyes. There were no spontaneous venous pulsations. Automated perimetry revealed supranasal defects, right eye worse that left. (Fig. 2).

Magnetic resonance imaging with and without gadolinium was normal. A lumbar puncture revealed an opening pressure of 150 mm H2O, no cells, protein less than 10 mg/dl, normal glucose, negative stains and cultures, and negative rapid plasma reagin (RPR). Complete blood count, chemistries, pregnancy test, thyroid function tests, RPR, fluorescent treponemal antibody (FTA), human immunodeficiency virus (HIV), cytomegalovirus (CMV), and urinalysis were all negative. The antinuclear antibody (ANA) was elevated at 1/320, but subsequent rheumatologic evaluation disclosed no specific collagen vascular disorders.

The day following the lumbar puncture, the patient reported increased energy, decreased desire to sleep, markedly reduced headaches, and she was able to participate in group activities. Her psychiatrist and nursing staff noted a decrease in her depressive symptoms, specifically decreased tearfulness, improved mood, increased energy and group attendance, and an absence of somatic complaints. She was discharged 7 days later with a BDI of 4. Twelve days following lumbar puncture, the patient was seen in neuro-ophthalmologic follow-up. She reported a recurrence of her headaches and psychiatric symptoms but her examination was unchanged. Fluorescein angiogram revealed bilateral disc leakage and no evidence of autofluorescence.

Four months later the patient had continued symptoms. Her weight had not fluctuated. Her examination was notable for progression of her visual field defects (Fig. 3). Repeat lumbar puncture revealed an opening pressure of 110 mm H2O, with normal CSF contents. Ten minutes after the lumbar puncture, the patient noted a decrease in her headache, and headaches did not recur until one week later. She was begun on Diamox 500 mg twice per day. One month later she reported an increase in her headaches. Her medications included Zoloft 150 mg/day, Diamox 500 mg twice per day and Ortho Novum 1/35. She still reported no transient visual obscurations and no diplopia. Her neuro-ophthalmologic examination was unchanged, with the exception of further visual field loss. Her Diamox was increased to 500 mg three times per day.

Five weeks later her symptoms and her visual fields were unchanged. Her weight had still not

FIG. 1. Left: right eye; right: left eye. Ophthalmoscopic appearance at presentation showing disc elevation, blurred margins, and mild hyperemia. (Green and Newman).
changed. Diamox was discontinued, and she was admitted to the hospital for bolt monitoring of her intracranial pressure. Over a 48-h period, bolt monitoring revealed ICP that fluctuated between 0 and 180 mm H₂O. No sedation was administered while the intracranial bolt was in place. When the bolt was placed, the patient reported a decrease in headache intensity. There was no notable CSF leak around the bolt. Two days after bolt placement an optic nerve sheath fenestration was performed through a standard medial orbitotomy (6). There were no complications. One day postoperatively her visual acuity was unchanged, and there was no diplopia. Her intracranial pressure was monitored for a 24-h period postoperatively and was noted to fluctuate between 0 and 80 mm H₂O.

One month postoperatively, the patient reported continued decrease in headaches since the surgery. She was still taking her Zoloft, and Ortho Novum 1/35, but was not on any Diamox. Her weight remained the same. Examination was notable for improvement in her disc edema (Fig. 4), and significant improvement in her visual fields (Fig. 5). The patient, her family, and her psychiatrist reported a dramatic improvement in her mood with resolution of her depressive symptoms. Her Zoloft was tapered and discontinued with no recurrence of her depressive symptoms. Over the subsequent 20 months, on no medications, without any weight change, the patient reported one mild headache per month and has remained euthymic. She has returned to school and has maintained a good sleep pattern and energy level. She has only sought medical attention for routine health care, and her neuro-ophthalmologic examination has remained stable.
DISCUSSION

We believe this case represents a form of PTC with two interesting features, namely normal intracranial pressure and presenting symptoms of depression relieved by PTC therapy. One of the strict Dandy criteria for PTC is increased intracranial pressure (1). Corbett has said that "under no circumstances should the diagnosis of PTC be made without finding elevated spinal fluid pressure . . . " (7). Normal intracranial pressure has been defined as 136 mm H$_2$O (SD ± 37.6) in patients of normal weight, and 167 mm H$_2$O (SD ± 36.46) in obese patients; however, it should be pointed out that there was no statistical difference between these two groups using Duncan's multiple range test (8). At no time was our patient documented to have an elevated CSF pressure, including two lumbar punctures and during two days of intracranial bolt monitoring. Johnston and Paterson (9) have observed wide fluctuations of CSF pressure in patients with PTC, using continuous ICP monitoring. Others have confirmed these fluctuations (10,11).

The medical treatment of PTC includes weight loss, carbonic anhydrase inhibitors, and possibly systemic steroids. If these modalities are unsuccessful in alleviating the symptoms or curtailing the visual dysfunction caused by PTC, then surgical intervention is indicated. Most authorities now agree that optic nerve sheath fenestration is the procedure of choice for progressive visual field loss and lumboperitoneal shunt the choice for intractable headaches with some overlap between the two (12-18). The importance of accurately diagnosing PTC is underscored by the fact that although these treatments are often highly effective, they are not without inherent side effects and complications (19,20).

We believe that our patient represents a variation of PTC that has been called "normal pressure
PTC.” Johnston et al., in a series of atypical PTC patients, reported a 13-year-old boy who was followed for four years after presenting with a unilateral scotoma (4). He had disc edema with progressive visual field and acuity loss, normal neurologic examination, and normal CT and MRI scans of the brain. His CSF pressure was 130 mm H2O at presentation with a normal composition. One year later CSF pressure monitoring via lumbar subarachnoid catheter was normal over a 36-h period. The patient’s visual fields and acuity declined and, after treatment with systemic steroids was ineffective, percutaneous lumboperitoneal shunt was performed. Surgery was successful in halting visual field loss, and there was rapid resolution of disc edema. Two episodes of recurrent disc edema and worsening of visual acuity were associated with shunt obstructions, both resolving with shunt revision.

This case was very similar to ours in that both patients were felt to have PTC without having a measured elevated ICP even with continuous ICP monitoring. Both patients had relief of their visual deterioration and resolution of their optic disc swelling after CSF diverting procedures. Johnston et al. proposed two possible explanations for the presence of papilledema in the absence of measured elevated ICP. Firstly, it was proposed that the situation could be likened to normal-pressure hydrocephalus, in which there is a definite abnormality of CSF circulation and volume relieved by drainage, without a demonstrable abnormality of CSF pressure (4,21). Secondly, it was hypothesized that local abnormalities in the region of the optic nerve sheath are responsible for the development of papilledema, with relatively normal ICP allowing a local buildup of pressure that is not reflected in the pressure measurement elsewhere in the subarachnoid space (4). It is possible that both these mechanisms played a role in our patient's clinical course. The former theory may have more merit than the latter, as our patient had other nonvisual symptoms that resolved upon optic nerve sheath fenestration, including relief of headache, and improvement in her psychiatric symptoms. Our case supports the theory that unilateral optic nerve sheath fenestration acts as a CSF filter (14,22). The patient had bilateral improvement in her visual fields and bilateral resolution of her papilledema. This bilateral effect after unilateral surgery has been reported in up to 73% of cases in other series (15-18). The continuous ICP monitoring also reflected a lower average ICP postoperatively. Her clinical course and response to treatment were typical of PTC. It is likely that certain patients have different susceptibilities to varying levels of ICP.

On four separate occasions (two lumbar punctures, subarachnoid monitor placement, and ultimately optic nerve sheath fenestration), our patient experienced improvement in her headaches as well as her depressive symptoms. We believe that there was an undetectable amount of CSF that leaked around the subarachnoid monitor. This is a known effect that occurs with the placement of these types of monitors (23). If the bolt had a tight seal, we would not have expected persistent headache relief with its insertion. Failure to document an elevated pressure could have been due to leakage around the subarachnoid monitor.

This improvement in her headaches and depressive symptoms was noted subjectively by the patient, and following the initial LP, by both the patient and her psychiatrist. While temporally related, it is unlikely that the reduction in her headaches alone accounted for her improved mood. The patient's primary complaints focused on her depressive symptoms and the headaches and eye pain were elicited only on a careful review of systems. It is reasonable to assert that the headaches may have contributed to the clinical presentation and decline in function; however, the patient's salutary improvement in numerous aspects of her life are difficult to attribute to alleviation of the subjectively mild headaches. It is possible that other confounding factors such as the placebo effect of her treatments and a desire to please her physician may have contributed to the relief of her headaches and depressive symptoms. Such confounds are equally unlikely since the patient had been involved in a therapeutic relationship with a previous psychiatrist and had failed to respond to antidepressant treatment. In addition, the course of psychiatric treatment with an antidepressant mechanistically very similar to previous medications, the relatively short duration of such treatment, and the maintenance of a euthymic state suggests a relationship in this patient between PTC and depressive symptoms.

Our patient met diagnostic criteria for major depression (24), and her symptoms were consistent with the atypical subtype of major depression. While her initial BDI score was mild to moderately severe, the BDI does not reliably assess patients with atypical symptom patterns. Furthermore, the patient demonstrated considerable social, academic, and occupational impairment indicative of a major affective disorder. The majority of these symptoms were relieved transiently by lumbar punctures and persistently by optic nerve sheath fenestration. The classic symptoms and signs of
48-h continuous subarachnoid ICP monitoring and we believe that a patient presenting with a clinical picture indicative of PTC, including neck stiffness, tinnitus, distal extremity parasthesias, joint pains, low back pain, and gait ataxia (3). Lessell (25), in his major review of pediatric PTC, reported that young children, excluding adolescents, may present with symptoms of irritability. He also cited the case of an infant with PTC who presented with somnolence (26). Other investigators have noted the association of PTC and psychiatric impairment (27,28). We feel that this case illustrates that clinical depression can be a presenting complaint of PTC and should be listed as another "minor symptom" of PTC. The preference of both PTC and depression to present in women during their childbearing years underscores the need to investigate the relationship between these two diseases.

The visual sequelae of untreated PTC can be devastating. Approximately 90% of patients with this disorder have some visual field defect, in at least one eye, and serious visual field loss or loss of visual acuity is seen in approximately 10–25% of carefully studied patients (2,12,29). Diagnosis and prompt therapy may be visually preserving. We believe that a patient presenting with a clinical picture indicative of PTC (complying with the modified Dandy criteria), without evidence of ICP greater than 180 mm H₂O on at least two separate measurements, should undergo more aggressive evaluation. If clinical signs or symptoms are unresponsive to established tolerable medical therapy, 48-h continuous subarachnoid ICP monitoring must be considered. If the three separate ICP measurements including the subarachnoid monitor have all been 180 mm H₂O or less, the diagnosis of "normal pressure pseudotumor cerebri" should be made. An accurate prevalence of this particular variant is unknown.

REFERENCES

Improvement in Visual Function in an Eye with a Presumed Optic Nerve Sheath Meningioma after Treatment with Three-Dimensional Conformal Radiation Therapy

Andrew G. Lee, M.D., Shiao Y. Woo, M.D., Neil R. Miller, M.D., Avinoam B. Safran, M.D., Walter H. Grant, Ph.D., and E. Brian Butler, M.D.

The treatment of optic nerve sheath meningiomas (ONSM) is controversial. Radiation therapy has been used with some success in patients with progressive visual loss. We report a case of visual improvement in a patient with an optic nerve sheath meningioma and progressive visual field loss, treated with conformal radiotherapy.

Key Words: Optic nerve sheath meningioma—Radiation—Meningioma.

Primary optic nerve sheath meningiomas (ONSM) are uncommon tumors and account for only 1–2% of all meningiomas. Dutton (1) reviewed the literature on these tumors in 1992 and reported a mean age at presentation of 40.8 years (age range 2.5–78 years), a female predominance (61%), and a unilateral tumor in 95% of cases (1). The clinical features of ONSM include progressive loss of visual acuity or visual field (96%), proptosis (59%), optic disc abnormalities (98%) such as chronic disc swelling (48%) or optic atrophy (49%), and optociliary veins (30%) (1). Computed tomographic (CT) and magnetic resonance (MR) scans have allowed the diagnosis of ONSM to be made in many cases without tissue biopsy (1–4). Although management of these tumors is somewhat controversial, conservative treatment is usually preferred due to the characteristic slow and indolent growth pattern of ONSM and the extremely low tumor-related mortality rate. Radiation therapy has been reported with some success in a number of reports (1–11). We report improvement in visual field loss in a patient with ONSM after treatment with conformal radiotherapy.

CASE REPORT

A 43-year-old white woman was found to have asymptomatic swelling of the left optic disc during a routine eye examination in February, 1991. Past medical, surgical, and ocular histories were unremarkable. Family history was significant for a sister with multiple cafe-au-lait spots but no other stigmata of neurofibromatosis type 1.
FIG. 1. Axial T1-weighted MR image after administration of gadolinium-DTPA contrast material shows enhancement of the optic nerve sheath on the left side (arrow).

The patient was in her usual state of good health until February, 1991, when during a routine ophthalmologic examination, she was found to have optic disc swelling in the left eye. She was referred to one of us (A.B.S.), who found normal visual acuity, color vision, visual field, and motility examinations in each eye and confirmed the left-sided optic disc swelling. CT and MR scans of the head and orbits revealed an enlarged optic nerve on the left that was thought to be consistent with an optic nerve sheath meningioma (Fig. 1). In May, 1991, the patient was noted to have 1.5 mm of proptosis and mild persistent optic disc swelling in the left eye, but the remainder of the neuroophthalmologic exam was unchanged. Over the next 2 years, the patient's visual acuity remained 20/15 in both eyes, and serial MR scans showed no change in the size or shape of the lesion.

In January, 1992, visual field testing in the left eye revealed a mild inferior defect. By June, 1993, the visual field defect was increased in size. On December 12, 1994, the patient was evaluated by one of us (N.R.M.), at which time the neuroophthalmologic examination revealed a normal right ocular fundus. The patient was orthotropic at distance and near in the primary gaze position, but developed an esotropia of 8 prism dipters in gaze to the left. Slit-lamp examination was normal in each eye. General physical examination was normal, and, specifically, she had no cafe-au-lait spots or axillary freckles. Hertel exophthalmometry measured 16 mm in the right eye and 18 mm in the left eye at a base of 94 mm. Ophthalmoscopy revealed a normal right ocular fundus. In the left eye, there was mild swelling of the optic disc associated with a single optociliary retinochoroidal shunt vessel (Fig. 3). A variety of management options, including observation, conventional radiotherapy, conformal radiotherapy, hormone therapy, and surgery were discussed with the patient.

The patient elected to undergo conformal radiation therapy using the Peacock System (12). This system creates optimized, three-dimensional, highly conformal dose distributions using an inverse solution that requires intensity modulated beams (13). The radiation is delivered using a multivane collimator (Fig. 4) that is placed in the accessory tray holder of the linear accelerator.

To insure accuracy in radiation treatment delivery, the head of the patient must be immobilized during treatment sessions. This immobilization system consists of two screws attached to the vertex of the cranium, into which a removable alumi-
num bar is attached (Fig. 5). For CT planning and treatment, this bar is coupled to an adjustable vertical bracket attached to the head of the treatment couch (Fig. 6). After each treatment, the bar is removed from the patient’s head, leaving only the two small fixation screws on the patient’s cranium. Cleaning of these screw sites is performed daily with peroxide and iodine as well as a daily dressing change.

Radiation is then planned and delivered in segmental arcs, much like a standard CT scan. Phantom film dosimetry to confirm the treatment plan is carried out before the actual treatment begins. As the gantry rotates around the patient, each of 40 small “beams” defined by the collimator is turned on or off by the movement of its vane for a variable period of time during each 5° of arc. This permits spatial modulation of the beam intensity through temporally variable attenuation of the treatment beam. After each arc, the couch table top of the linear accelerator is indexed at a precise distance, and another arc is then delivered. The indexing is accomplished with a customized device that attaches to the side rails of the treatment couch and has digital readout in hundredths of a millimeter. Figure 7 shows the isodose distribution of radiation for this patient’s tumor. The tumor receives the maximum dosage (5233 cGy), whereas the contralateral optic nerve and surrounding brain receive much lower dosages of radiation than the target. In our patient, the total dose of radia-

FIG. 3. Optic disc photograph of the left eye shows mild disc edema and a possible optociliary shunt vessel inferiorly at 6 o’clock (arrow).

FIG. 4. Multivane collimator of Peacock system.

FIG. 5. Attachment of patient’s head to treatment couch.

FIG. 6. Patient is positioned and aligned during treatment session.
tion delivered to the tumor was 5040 cGy given in 180 Cgy fractions over a 6-week period of time.

One week after the completion of treatment, on March 7, 1995, the neuro-ophthalmologic examination revealed a visual acuity of 20/15 OD and 20/15 OS. Color vision was 14 of 14 in each eye using Ishihara color plates. The optic disc swelling on the left side was unchanged. Static perimetry of the left eye showed a mean deviation of only —2.21 db, associated with a mild inferior defect (Fig. 8).

DISCUSSION

The treatment of ONSM remains controversial; however, the use of radiotherapy in patients with documented progressive visual loss has been gaining wider acceptance. Visual improvement was reported, in the literature review by Dutton (1), by 12 of 16 (75%) patients treated with conventional radiation therapy.

Treatment of ONSM with conventional radiation therapy also exposes the optic chiasm and contralateral optic nerve to radiation however, resulting
in radiation-induced necrosis in up to 15% of patients (9,11). Sarkies (4) reported a patient with bilateral ONSM treated with conventional radiation therapy of 1325 cGy to both orbits and chiasm in whom therapy was terminated prior to completion because of progressive visual loss believed to be due to radionecrosis (4). Thus, more precise radiotherapeutic modalities are desirable when treating these histologically benign tumors. Few reports describe the use of precision radiation techniques in the treatment of optic nerve sheath meningiomas (8). The present report is the first report, to our knowledge, of treatment of an ONSM with three-dimensional conformal radiotherapy (Peacock). This technique employs plan optimization by computer analysis and intensity modulation of the radiation beam during treatment to maximize delivery of radiation dose to the tumor and minimize the dose to surrounding tissues. Conformal three-dimensional radiotherapy may be an alternative to conventional radiotherapy for the treatment of ONSM, and may prove to have equal efficacy with improved safety when compared to conventional therapies.

REFERENCES
Chiasmal Herniation as a Complication of Bromocriptine Therapy

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Introduction: Medical treatment of macroadenomas with dopamine agonists decreases tumor mass and improves visual defects. We report an unusual complication of a macroadenoma responding to bromocriptine: a visual field defect caused by downward herniation of the optic chiasm.

Materials and Methods: A 64-year-old woman was found to have a 4.5 cm macroadenoma with superior displacement of the optic chiasm, bitemporal hemianopia, and serum prolactin concentration (P) of 17,060 μg/L. Bromocriptine was initiated at 2.5 mg/day and increased to 7.5 mg/day over 2 months.

Results: After 2 months, visual fields improved significantly and tumor height decreased to 3 cm with resolution of the optic chiasm displacement. P decreased to 1,180 μg/L. After 5 months of therapy, visual fields were normal, and P was 8 μg/L. After 8 months of therapy, new bilateral visual defects were observed. Magnetic resonance imaging (MRI) revealed further decrease of the tumor height to 1.5 cm, and inferior and lateral traction of the optic chiasm as the probable mechanism for the new visual field deficit. P was <1 μg/L. Bromocriptine was decreased to 5 mg/day to allow reduced traction on the optic chiasm and its blood supply. Over the next 4 months, visual field abnormalities resolved.

Conclusions: We report the development of a visual field abnormality that is explained by chiasmal herniation caused by a shrinking macroadenoma. This complication resolved with a decrease in the bromocriptine dose. We suggest that patients undergoing bromocriptine therapy for macroadenomas be followed for this potential complication.

Key Words: Macroprolactinoma—Bromocriptine—Visual field defect—Optic chiasm—Prolactin.

The medical treatment of pituitary macroadenomas with ergot alkaloids is a well-accepted form of therapy. The use of bromocriptine therapy results in tumor shrinkage in 90% of cases (1,2). Tumor size reductions of ≥50% occur in 40–85% of cases (3). Serum prolactin concentrations (P) fall to <10% of pretreatment values in 90% of patients and normalize in 66% (1). Bromocriptine therapy leads to visual field improvement in 80–90% of patients with significant visual field abnormalities (4). These visual improvements often precede radiologic evidence of tumor shrinkage (4). In general, bromocriptine is without significant complications.

We report an unusual complication associated with bromocriptine therapy and reduction in tumor size. In a patient with a large macroadenoma being treated with bromocriptine, we observed the expected resolution of significant visual field defects followed by the unexpected development of new visual field defects. The development of new visual field defects in a patient responding to bromocriptine with tumor shrinkage is a previously unreported complication. The potential mechanism and successful treatment are described.

CASE REPORT

A 64-year-old white woman was referred for a macroadenoma. She developed amenorrhea at age 27 years after the birth of her last child. Galactorrhea was not present, and the etiology of the amenorrhea remained undetermined. Hypothyroidism was diagnosed soon thereafter, and thyroxine replacement was begun at 0.075 mg/day. Family history was negative for kidney stones, hypercalcemia, or excessive peptic ulcer disease.

Headaches and decreased visual acuity with loss
of the temporal half of the right visual field developed gradually after age 61 years. Generalized pain and shoulder stiffness, along with an elevated sedimentation rate, led to a diagnosis of polymyalgia rheumatica within the same year. She was treated with prednisone and felt better on a maintenance dose of 5 mg/day. Due to persistent visual complaints computed tomography (CT) and magnetic resonance imaging (MRI) scans were ordered at age 64 years and revealed a homogeneous mass with some calcification and a height of 4.5 cm. It extended from the suprasellar cistern to the pre-pontine cistern, with destruction of the clivus and sphenoid wing, and extension to the nasopharynx. Subsequent biopsy through the nose disclosed a prolactinoma; initial serum prolactin concentration was 17,060 µg/L. Visual fields revealed severe bitemporal hemianopia. Visual acuity was 20/30 OD and 20/25 OS. Ophthalmoscopic examination showed moderate pallor of the optic nerves bilaterally, right greater than left. Thyroid stimulating hormone (TSH) was 0.2 mU/L (reference range 0.7-5.0), T₄ was 116 nmoles/L (reference range 59-152), T₃ resin uptake ratio was 0.94 (reference range 0.89-1.17), follicle stimulating hormone (FSH) was 9 U/L (reference range for postmenopausal women 35-151), and luteinizing hormone (LH) was 0.8 U/L (reference range for postmenopausal women 10.8-61). Serum concentrations of growth hormone, IGF-1, ionized calcium, and phosphorus were normal.

MATERIALS AND METHODS

Hormone assays

TSH was measured by immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA, U.S.A.); radioimmunoassays (RIA) were used for measurement of serum concentrations of prolactin (kit from Diagnostic Products Corp., Los Angeles, CA, U.S.A.); growth hormone (kit from Sanofi, Arlington Heights, MN, U.S.A.); FSH and LH (kit from CIBA-Corning, Norwood, MA, U.S.A.) and total T₄ (kit from CIBA-Corning Diagnostic, Medfield, MA, U.S.A.). IGF-1 was measured by extraction RIA (Nichols Institute). Ionized calcium was measured by ion analyzer (CIBA-Corning). Phosphorus was measured by spectrophotometry.

Visual fields

Visual fields were measured using a 30-2 threshold test on an automated Humphrey perimeter. Visual field results are reported as Gray scale, and total and pattern deviations. Each point in the total deviation represents the average over 6° of the visual field and has been compared to a group of age- and acuity-matched controls. The severity of the defect at each point is expressed as a statistical deviation from the mean of the control group and, thus, has an attached confidence interval. Two statistical measures were used to evaluate changes in the patient's visual fields over time; mean deviation (MD) and change in probability (Statpac 2 Glaucoma Change Probability program). The MD compared the patient's visual field to a group of age-matched controls; change in probability compared a single visual field to a baseline established by the initial two visual fields performed by the patient. The standard deviation for the MD was -3.2 db (p = 0.05) and was -3.0 db for the change in probability. This suggested that the patient's reliability was excellent and not different from a group of age-matched controls.

RESULTS

The initial MRI results and visual field abnormalities are summarized in Fig. 1. Bromocriptine was initiated at 2.5 mg/day for 4 days and then increased to 5 mg/day for 2 months. Within 2 days of initiation of therapy, the patient reported subjective improvement in her vision and decreased severity of her headaches. Within 1 month, P decreased to 3,008 µg/L. Within 2 months, the tumor height decreased to 3 cm (Fig. 2), and visual field examination improved dramatically. After 2 months of bromocriptine therapy at 5 mg/day, bromocriptine was increased to 7.5 mg/day. Over the next 3 months (5 months since initiation of therapy), P decreased to 8 µg/L, and visual field defects gradually resolved (Fig. 2); 3 months later (8 months of bromocriptine therapy), a worsening of visual fields occurred in both eyes (Fig. 3). In the left eye, this deterioration reached statistical significance. The MD (measure of the patient versus age-matched controls) declined from a previous value of -0.62 db to -3.04 db, which was not statistically different from the pretreatment level of -5.16 db using the change in probability measure (compares fields for a single patient). The right eye MD was -2.05 db, which was much better than the pretreatment value of -14.08 db, but was still worse than the patient's field 2 months earlier (MD -0.54 db). P was undetectable. Ophthalmoscopic examination revealed mild temporal pallor OD and bowtie atrophy OS (pallor of the temporal and nasal portions of the optic nerve suggestive of chiasmal compression). MRI revealed further involution.
of the tumor with herniation and angulation of the optic chiasm (Fig. 3). To allow for decreased traction on the optic nerve and/or its blood supply, bromocriptine was decreased to 5 mg/day. The field defects in both eyes recovered gradually with lowering of the bromocriptine dose. One month after the decrease of the bromocriptine dose, the MD was −2.04 db OS and −1.24 db OD. By the end of 2 months, the left visual field continued to improve and, at that time, was not statistically different from the field obtained after 5 months of bromocriptine therapy (MD of −0.91 versus −0.62 db). The visual improvement was maintained, and 4 months after decreasing the bromocriptine dose from 7.5 to 5.0 mg/day, the visual fields were almost normal OS with an MD of −0.13 db, and showed only slightly decreased temporal sensitivity OD (MD of −0.75) compared to those of age-matched controls. Tumor height remained unchanged and P remained undetectable (Fig. 4). The changes in MD over the course of therapy with bromocriptine are shown in Fig. 5. These results show that the patient’s vision improved initially on bromocriptine, worsened after 6 months of bromocriptine therapy, and then gradually improved after the dose of bromocriptine was decreased.

**DISCUSSION**

We report a visual field defect caused by herniation of the optic chiasm induced by a shrinking macroprolactinoma. The macroprolactinoma initially responded to bromocriptine therapy with the expected significant decrease in size, and the initial visual field defects resolved completely. However, following resolution of the visual field defects, new visual field defects developed unexpectedly during therapy with bromocriptine. The most likely explanation for this new visual field defect was herniation of the optic chiasm in an inferior and left direction. This complication has not been reported previously in a prolactinoma responding to bromocriptine. Several observations and statistical analysis demonstrated that the new visual field abnormality was not an artifact of testing. Sequential testing revealed new bitemporal visual field deficits 6 months after initiating bromocriptine. When the bromocriptine dose was decreased,
the new deficits resolved over the next 4 months. The occurrence of this new visual abnormality could not be explained by noncompliance with therapy, since P was undetectable at the time of this complication. Decreased tumor responsiveness to bromocriptine was also unlikely, as MRI demonstrated that the prolactinoma was continuing to decrease in size.

Loss of vision in association with an empty sella is usually, but not always, due to herniation of the optic chiasm (5-9). Herniation of the optic chiasm has previously been reported following surgical excision, radiation therapy, or a combination of the two in patients with macroadenomas (5,9). Additional causes of the chiasmal syndrome include antibiotic therapy for tuberculous meningitis (6), transsphenoidal hypophysectomy for breast cancer (7), transsphenoidal emptying of a Rathke's

FIG. 2. Visual field examination after 5 months of bromocriptine therapy, and MRI after 2 months of bromocriptine therapy. After 2 months of bromocriptine therapy, the prolactinoma height had decreased to 3 cm, and the optic chiasm was no longer bowed upwards. P was 8,008 μg/L. Visual fields were improved markedly at this time (not shown) and, as shown, had returned almost completely to normal after 5 months of bromocriptine therapy. The patient still had a small parafoveal bitemporal hemianopia as indicated in the total deviation. P was 8 μg/L.

FIG. 3. Visual field examination and MRI after 8 months of bromocriptine therapy. After 8 months of bromocriptine therapy, the height of the prolactinoma had decreased to 1.5 cm, and inferior traction and angulation of the optic chiasm had developed. New visual parafoveal and peripheral field defects had developed involving opposite surfaces of the chiasm, inferior on left (superior defect) and superior on right (inferior defect). Bromocriptine dose was 7.5 mg/day and P was not detectable.
cleft cyst (5), sarcoidosis (9), and postpartum pituitary necrosis (9). Visual field defects included bitemporal hemianopia, unilateral temporal field cut, and virtual blindness in one eye with hemianopia in the other (5). Most patients are managed surgically. In a series of 11 patients, this resulted in improved vision, although there were persistent visual field abnormalities in eight patients (5). Surgical treatment involved elevation of the diaphragm by packing of the sella in three patients, lysis of adhesions or incision of the diaphragm in three patients, and placement of a hole in the lamina terminalis in one patient (5).

Surgical treatment in the patient we describe was considered; however, we elected a conservative approach. The rationale was to reduce traction on the optic nerve and/or its blood supply by reducing the bromocriptine dose to allow slight tumor re-expansion. We chose not to continue the current bromocriptine dose or to increase it, since further shrinkage of the tumor could cause worsening visual field defects. Within 4 months of lowering the bromocriptine dose (7.5 to 5.0 mg/day), perimetry returned to normal. P remained undetectable and tumor height remained at 1.5 cm. These improvements persisted. It is of interest that the visual fields improved without detectable re-expansion of the tumor on MRI scan. This experience is similar to the course of visual field improvement in shrinking prolactinomas and other pituitary tumors; visual defects often improve without or prior to radiologic changes (10). This suggests that the effect of the traction on the optic chiasm and/or its blood supply can be relieved by small changes in tumor size that are undetectable by MRI. Ischemia to the optic chiasm has been demonstrated to cause visual field defects in primary empty sella syndrome (8). Moreover, ischemic chiasmal syndrome with or without herniation can also result from mechanical compression on the optic chiasm, optic nerve junction, or both (9). It is likely that relief of ischemia occurs with a small change in tumor size. Therefore, for the first time, we were able to treat a chiasmal
syndrome medically by titrating the bromocriptine dose.

Although the mechanism of optic nerve herniation is not clear, there are two possibilities: to account for this prolapse and traction. The optic chiasm may have prolapsed into the space vacated by the shrinking prolactinoma or it may have been pulled down by its attachment to the shrinking prolactinoma. Herniation from a shrinking mass is usually perceived to be due to traction (5-7,11). For traction to occur, there must be some mechanism to explain attachment of the chiasm to the tumor. This macroadenoma was, likely, of longstanding duration. It probably was present at age 27, when the patient developed amenorrhea. Over the years prior to diagnosis, the patient may have developed adhesions or scarring that attached the chiasm to the prolactinoma. The presence of calcifications in the tumor suggests previous hemorrhage and scarring and supports this possibility. The second possibility is that bromocriptine-induced shrinkage was responsible for fibrosis and, thus, attachment of the prolactinoma to the optic chiasm. Bromocriptine-induced fibrosis associated with tumor shrinkage has been identified in resected prolactinomas that had been pretreated with bromocriptine (12-15). Therefore, in theory, it is possible that attachment of the optic nerve to the tumor occurred secondary to bromocriptine-induced tumor fibrosis. However, this latter possibility seems less likely, since chiasmal herniation with bromocriptine therapy is so rare. If bromocriptine were the cause of attachment of the optic chiasm to the prolactinoma, then chiasmal herniation would be observed more commonly. Therefore, it seems most likely that the attachment of the optic nerve to the tumor occurred prior to treatment with bromocriptine.

In summary, we have described the development of a new visual field defect caused by herniation of the optic chiasm in a subject with a prolactinoma that was shrinking in response to bromocriptine. This new defect responded to a decrease in the bromocriptine dose. To our knowledge, this case represents a previously unreported complication of bromocriptine-induced tumor shrinkage and the first report of medical management of a chiasmal syndrome. We conclude that patients receiving bromocriptine therapy for macroadenomas should be followed carefully for development of new visual defects, even when the tumor is shrinking and initial defects are resolving.

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REFERENCES

Bilateral Ptosis due to Mesencephalic Lesions with Relative Preservation of Ocular Motility

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Three cases of bilateral ptosis with relatively normal ocular motility are presented. In two of the patients, neuroimaging demonstrated lesions in the region of the third cranial nerve subnuclei. These unusual clinical presentations are due to isolated involvement of the central caudal nucleus supplying the bilateral levator muscles, with virtually complete sparing of other third cranial nerve structures.

Key Words: Ptosis—Bilateral—Third cranial nerve—Central caudal nucleus.

In 1953, Warwick demonstrated that the oculomotor nucleus in monkeys is arranged as discrete subnuclei, with the central caudal nucleus providing a common output to both levator palpebrae muscles (1). We present three cases of bilateral ptosis with relative preservation of other third cranial nerve functions. Magnetic resonance imaging (MRI) demonstrated lesions in the area of the third-nerve nuclear complex in two patients. The third patient had definite multiple sclerosis and scattered white-matter lesions, although no lesion was visible in the third-nerve complex on neuroimaging. We suggest that the bilateral ptosis in each of these cases is secondary to relatively isolated involvement of the central caudal nucleus, thus providing further clinical evidence that Warwick's scheme of oculomotor nuclear organization holds true for humans.

CASE REPORTS

Case 1

A 67-year-old man was unable to open his eyes when he awoke in the morning. Eleven years earlier, he had had a posterior fossa arachnoid cyst with hydrocephalus that was treated with a cystoperitoneal shunt, resulting in a gaze-directed nystagmus. He had a history of esotropia and amblyopia of the left eye. One year before his presentation with ptosis, he developed cervical and inguinal lymphadenopathy, and a cervical lymph node biopsy demonstrated non-Hodgkin large-cell lymphoma. Bone marrow biopsy and chest and abdominal computed tomography (CT) were negative. He was treated with seven cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and was judged to be in complete remission.
At examination, he had complete bilateral ptosis (Fig. 1). Motility was normal with the exception of a (longstanding) mild right abduction deficit and moderately deficient upgaze (Fig. 2). Downbeat nystagmus was present in the primary position. Visual acuity was 20/50 in the right eye and 20/300 in the amblyopic left eye; slit-lamp examination showed mild bilateral cataracts. Visual fields were full to confrontation. The ophthalmoscopic examination yielded normal findings. The pupils were 2 mm bilaterally and constricted to light and near, and there was no relative afferent pupillary defect.

Examination of cranial nerves II–VII yielded otherwise normal findings. Extremity strength and sensation were normal. He had slight dysmetria bilaterally and a wide-based ataxic gait.

Cranial CT demonstrated postoperative changes in the posterior fossa, where a large cyst communicated with the fourth ventricle. The shunt was functioning normally. MRI of the brain showed abnormal signal intensity in the periaqueductal area on T2-weighted imaging, which was enhanced by the administration of gadolinium (Fig. 3), with additional enhancement in the left globus pallidus and the floor of the third ventricle.

All blood studies, electrocardiography, and chest radiography were unremarkable. Cerebrospinal fluid had nine lymphocytes per mm$^3$ with normal cytology. Cerebrospinal fluid protein, glucose, and cryptococcal antigen were all normal, and there was no growth on routine and fungal cultures. A repeat lumbar puncture 24 h later yielded normal findings. Edrophonium chloride (10 mg) was administered, but did not improve the ptosis.

Although the ptosis improved considerably over the next several weeks, within a month, the patient had developed lower extremity weakness and ataxia. Subsequent MRI revealed additional en-
FIG. 3. Case 1. A: MRI demonstrates abnormal signal intensity in the periaqueductal grey matter on T2-weighted imaging, [echo time (TE) 100, resonance time (TR) 2000]. The abnormality is not visible on T1 imaging (TE 20, TR 535), but is evident with gadolinium enhancement (B).

hancing lesions in the brain, and a stereotactic biopsy confirmed the presence of lymphoma. Whole-brain irradiation was initiated, but progressive neurologic deterioration resulted in his death 8 months later.

Case 2

A 70-year-old woman with known breast cancer metastatic to the brain presented with a 6-week history of increasing difficulty in opening her eyes. She had been admitted to the neurosurgery service 5 months earlier because of increasing headache, memory loss, and ataxia; at that time, MRI revealed a cystic mass in the region of the quadrigeminal plate with compression of the Sylvian aqueduct and secondary hydrocephalus of the third and lateral ventricles. She had a vertical gaze disturbance, but no ptosis. Placement of a ventriculoperitoneal shunt resolved her symptoms. Further workup revealed an infiltrating ductal carcinoma in the left breast that was treated with a modified radical mastectomy; none of nine biopsied lymph nodes was positive. The brainstem lesion, presumably metastatic, was treated with radiation therapy (a total of 3,500 rads in 14 fractions to the whole brain).

On presentation, the patient reported that she had not been able to see for the prior 6 weeks without manually holding her eyelids open, and that her vision was somewhat blurred; both the ptosis and the blurring were worse in the morning and improved somewhat as the day progressed. She had no complaints of headache, nausea, vomiting, diplopia, or systemic weakness. Dexamethasone tablets, which she had begun taking 4 weeks before her visit, had helped the ptosis, which was always present to some degree.

Current medications included prazosin hydrochloride for systemic hypertension, oxazepam, and dexamethasone.

On examination, she had bilateral ptosis slightly greater on the right (Fig. 4), with full ocular motility (Fig. 5). Visual acuity was 20/20 in both eyes,

with normal findings on pupillary examination, visual field, slit-lamp, and fundus examinations. MRI revealed a 1.5-cm cystic mass, associated with the quadrigeminal plate with a midbrain signal abnormality (Fig. 6), but there was no obvious progression from her previous scans.

Over the next 4 months, her ptosis became more profound and was accompanied by decreased hearing and speech difficulties. Neuroimaging then showed marked enlargement and progression of the midbrain mass, and the patient underwent a left occipital craniotomy via a transtentorial approach to the pineal region for debulking of the tumor, followed by additional radiation to the brain, chemotherapy, and hormone therapy. Her profound bilateral ptosis was present until her death, which occurred 7 months after her initial presentation.

Case 3

A 41-year-old woman with a 9-year history of relapsing/remitting multiple sclerosis presented with increasing bilateral ptosis for 2 days. She had no diplopia, and neurological review of systems showed no abnormal findings other than chronic intermittent paresthesias of the face and limbs.

She had episodic urinary incontinence, as well as an optic neuritis in the right eye that had developed 2 years earlier. She had taken cyclophosphamide and methotrexate in the past; at presentation, she was taking 20 mg/day of prednisone.

Neuro-ophthalmic and neurologic examinations showed no abnormalities other than bilateral flaccid ptosis (Figs. 7 and 8). Administration of edrophonium chloride did not alter her ptosis.

MRI of the brain showed abnormal signal within the periventricular white matter, superior to the frontal horns, adjacent to the left occipital horn, and within the left substantia nigra and parieto-occipital area. No periaqueductal mesencephalic lesion could be identified. Lumbar puncture showed no abnormalities.

The patient’s ptosis was believed to be secondary to an exacerbation of her multiple sclerosis, and she was admitted to the hospital for a course of parenteral adrenocorticotropic hormone (80 U/day). Within 2 days, improvement in lid function was noted, and within a week, her ptosis had...
FIG. 6. Case 2. A: MRI at presentation demonstrates a cystic mass in intimate association with the quadrigeminal plate on sagittal T1 image (TE 25, TR 535). B: Axial T2 image (TE 100, TR 2000) shows the periaqueductal midbrain signal abnormality produced by the mass and surrounding edema, and hydrocephalus with presumed transependymal flow of cerebrospinal fluid (CSF).

disappeared. Although she has had additional exacerbations of multiple sclerosis during the 4 years since her initial presentation, she has had no recurrence of her ptosis.


DISCUSSION

Warwick's studies using retrograde chromatolysis of the cells of the oculomotor complex of monkeys demonstrated discrete subnuclei, arranged in a rostro-caudal fashion (1). A central caudal nucleus provided bilateral innervation to the levator palpebrae muscles. Other subnuclei, serving the parasympathetic innervation to the pupillary sphincter, the inferior oblique, as well as to the medial, inferior, and superior recti, were paired, innervating ipsilateral third cranial nerve components. Paired superior rectus subnuclei had decussating efferent outflow, innervating the superior rectus contralaterally. There is ample clinical evidence to suggest a similar arrangement in humans, with reports of discrete periaqueductal midbrain lesions affecting certain third-nerve functions while entirely sparing others (2–8).

In addition to our three cases, we have discovered additional reports of relatively isolated midbrain ptosis, beginning with Stevenson and Hoyt's description of bilateral ptosis associated with minimal adduction weakness in the left eye of a patient with breast cancer metastatic to the midbrain (9). Conway et al. (6) described a 45-year-old man with isolated bilateral ptosis, who had discrete inflammatory lesions in the brain and brainstem and a lesion in the dorsal, midline aspect of the oculomotor complex. Meienberg et al. (10) reported the case of a 65-year-old man with apparent brainstem ischemia who eventually developed a "locked-in syndrome," but, at one point, exhibited bilateral ptosis with normal eye movements. Beck and Smith (11) described a 24-year-old man with bilateral ptosis and 4 diopters of left hypertropia on right gaze. MRI showed a mass in the region of the third nerve nucleus, presumed to be a brainstem glioma. Barton et al. (12) discusses a patient with acquired immune deficiency syndrome (AIDS) who presented with the acute onset of a bilateral complete ptosis and minimal vertical gaze disturbance. Neuroimaging revealed a periaqueductal
midbrain lesion (thought to be impinging on the central caudal subnucleus) and bilateral masses in the caudate nuclei. Neuropathology revealed that the midbrain lesion was most consistent with AIDS encephalopathy, although the caudate lesions showed lymphoma of B-cell origin.

We propose that the bilateral ptoses in our three patients were caused by lesions involving the median group of nerve cells supplying both levator muscles, i.e., the central caudal nucleus, with relative sparing of the remainder of the oculomotor subnuclei. In the first patient, recurrence of central nervous system (CNS) lymphoma was demonstrated, with a lesion in the periaqueductal gray matter. In the second patient, a metastatic breast lesion to the midbrain tectum was identified, with compression of the dorsal aspect of the oculomotor nuclear complex. In the third patient, who had definite multiple sclerosis, many white matter plaques were demonstrated on MRI, although a discrete plaque in the region of the central caudal nucleus/fascicles could not be seen with neuroimaging. The existence of such a lesion seems reasonable, however, as small active plaques frequently are not shown on MRI, and no other lesion or process can adequately explain the patient's symptoms. Furthermore, the remitting nature of the ptosis is consistent with multiple sclerosis.

Generally, lesions of the oculomotor complex affect multiple functions. The discreteness of the effect of a lesion on a single midline nucleus might suggest a vascular mechanism. However, as in our three cases, nonvascular causes represent the majority of reported cases of isolated midbrain ptosis, suggesting that there may be some structural predisposition of this nucleus to the effects of intrinsic lesions at this location.

REFERENCES

Idiopathic Hypertrophic Cranial Pachymeningitis: Clinical–Radiological–Pathological Correlation of Bone Involvement

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We present the clinical, radiological, and pathological findings in an elderly man who developed a progressive superior orbital fissure syndrome due to idiopathic hypertrophic cranial pachymeningitis. The unique aspect of this case concerned the increased density of the sphenoid ridge and lateral orbital wall observed by using computed tomography, and the enhancement of the marrow signal seen on magnetic resonance imaging. These neuroimaging abnormalities of bone resulted from an indirect nonspecific response of the marrow to the adjacent soft tissue and dural inflammatory process. Key Words: Pachymeningitis—Ophthalmoplegia—Optic neuropathy—Meningioma—Sphenoid.

Idiopathic hypertrophic cranial pachymeningitis is an unusual chronic inflammatory disorder of unknown etiology that causes deficits by mass effect and infiltration of neurologic structures adjacent to the involved dura (1). We present the following case report to emphasize a unique aspect of this disorder that concerned bone involvement identified by using computed tomography (CT) and magnetic resonance imaging (MRI). The pathological correlate of these neuroimaging abnormalities of bone was a nonspecific reactive change of the marrow in response to the adjacent inflammatory process affecting the soft tissues and dura. To the best of our knowledge, this case represents the first pathological report demonstrating bone involvement in idiopathic hypertrophic cranial pachymeningitis.

CASE REPORT

A 78-year-old man was referred for evaluation of a recently discovered right-sided retro-orbital mass lesion. Ten months earlier, he began experiencing progressive vertical diplopia. A dull headache developed above and behind his right eye 3 months before referral. He then noted progressive loss of vision of his right eye. Orbital CT revealed an enhancing soft tissue mass lesion extending from the right superior orbital fissure into the orbital apex, the inferior orbital fissure and pterygopalatine fossa, the anterior cavernous sinus, and along the greater wing of the sphenoid bone (Fig. 1). Increased density of the lateral wall of the orbit and greater wing of the sphenoid bone were also noted (Fig. 2).
HYPERTROPHIC CRANIAL PACHYMENINGITIS

FIG. 1. Computerized tomography in the axial plane revealing a right-sided enhancing soft tissue mass extending through the superior orbital fissure into the orbital apex (short black arrow) and into the middle cranial fossa along the greater wing of the sphenoid bone (long white arrow).

FIG. 2. Computerized tomography at a level similar to that depicted in Fig. 1, with window settings optimized for bone detail, revealing increased density of the greater wing of the sphenoid bone and lateral wall of the orbit on the right side (white arrow). Note the loss of anatomical distinction between the cortex and diploic space.

His visual acuity was 20/25-2 with marked dyschromatopsia in his right eye and 20/15 in his left eye. Goldmann perimetry revealed a generalized central depression and an inferior arcuate defect in his right eye. The right optic disc appeared slightly full and hyperemic. There was moderate right-sided ptosis and impairment of levator function, but without evidence of aberrant regeneration of the affected eyelid. Horizontal ductions and depression of the right eye were restricted. He had 4 mm of relative axial proptosis of his right globe. His corneal reflex and sensitivity were reduced on the right.

MRI revealed that the mass was isointense relative to brain on T1-weighted sequences (Fig. 3), and enhanced uniformly following administration of gadolinium (Fig. 4). The meninges of the middle cranial fossa and along the greater wing of the sphenoid bone were thick and demonstrated enhancement (Fig. 4). The marrow signal intensity of the sphenoid ridge, normally bright on T1-weighted images, was diminished on the right side (Fig. 3) and also demonstrated enhancement (Fig. 4).

His medical evaluation included a normal chest radiograph, an erythrocyte sedimentation rate (Westergren) of 47 mm/h, and normal results of Venereal Disease Research Laboratory and fluorescent treponemal antibody tests, angiotensin-converting enzyme assay, antinuclear and neutrophil-cytoplasmic antibody assays, rheumatoid factor assay, and serum protein electrophoresis analysis. Skin testing revealed no reaction against...
purified protein derivative, but positive reactivity against two control antigens. His cerebrospinal fluid contained three white cells/ml, protein 59 mg/dl (normal, 15-45 mg/dl), and negative Venereal Disease Research Laboratory and fluorescent treponemal antibody tests, cytology, cryptococcal antigen assay, and stains and cultures for bacteria, fungi, and tuberculosis.

He underwent a frontotemporal craniotomy and transcranial orbitotomy. The dura at the base of the skull was thick and indurated. The anterior clinoid and sphenoid wing appeared abnormally dense. The orbital apex and optic canal were decompressed. Bone and dura were submitted for pathological examination. The dura was thick, fibrotic, and revealed pachymeningitis with a lymphoplasmacytic infiltrate, most marked on the parenchymal surface (Fig. 5). Meningothelial hyperplasia was seen, but without features of a meningioma. The bone was irregular and the marrow spaces were replaced by fibrous tissue (Figs. 6 and 7). No direct infiltration of the inflammatory process between the dura and bone was observed. There were no granulomas or areas of vasculitis. Special stains for spirochetes and fungi were negative. Immunostains showed that the inflammatory population was polyclonal.

He was initially treated with azathioprine and intravenous pulse methylprednisolone followed by oral prednisone 60 mg daily. Azathioprine was discontinued within a few weeks due to a severe allergic reaction. He has been maintained on slowly tapering doses of oral prednisone alone for the past 24 months. His clinical findings improved to a moderate degree during the first few months of treatment and have since remained stable. MRI, repeated 6 and 18 months after the initiation of corticosteroids, demonstrated marked improvement in size and degree of enhancement of the lesion.

DISCUSSION

Hypertrophic cranial pachymeningitis can be associated with a variety of infectious and systemic inflammatory disorders, including syphilis (2), tuberculosis (3), rheumatoid arthritis (4), sarcoidosis...
HYPERTROPHIC CRANIAL PACHYMENINGITIS

(5), and Wegener's granulomatosis (6). Hypertrophic cranial pachymeningitis can also occur as an idiopathic disorder, either restricted to the intracranial compartment or as part of a systemic disorder associated with fibrosclerosis at multiple sites. The idiopathic localized presentation can develop as an extension of other sclerosing disorders affecting the skull base, including idiopathic sclerosing inflammation of the orbit (7,8) and some forms of the Tolosa-Hunt syndrome (9–11). The systemic disorder, often referred to as multifocal fibrosclerosis, encompasses some combination of idiopathic hypertrophic cranial pachymeningitis, idiopathic sclerosing orbital inflammation, retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, and Riedel's thyroiditis (12,13). The common denominator relating all of these presentations is a similar constellation of histopathological abnormalities, including desmoplasia and lymphoplasmacytic infiltration, as well as a similar immunohistochemical profile (14).

Many recently reported cases of idiopathic hypertrophic cranial pachymeningitis have emphasized visual loss and ophthalmoplegia due to predominant mass involvement of the parasellar and superior orbital fissure regions, similar to the case described herein (9–11,15,16). However, during our review of the medical literature, assisted by a computerized database (Medline, National Library of Medicine), we encountered only one report of...
possible bone involvement in this disorder (17). A 50-year-old man with chronic renal failure undergoing hemodialysis developed unexplained progressive visual loss, other cranial nerve deficits, and then a fatal intraparenchymal hematoma. Postmortem examination revealed diffusely thickened dura at the base of the skull consisting of granulomas, fibrosis, and chronic inflammatory changes. Gross erosion of the petrous portion of the temporal bone was noted, but without histopathological explanation (17).

In the present case, the increased bone density seen on CT, and bone marrow signal changes observed using MRI, were the indirect result of a nonspecific bone reaction induced by the adjacent dural inflammatory process. Bony destruction or direct lymphoplasmacytic infiltration was not observed.

REFERENCES

Neurosarcoidosis Presenting as an Intracranial Mass in Childhood

Hana Leiba, M.D., R. Michael Siatkowski, M.D., William W. Culbertson, M.D., and Joel S. Glaser, M.D.

A 13-year-old boy presented with bilateral panuveitis and a superior oblique palsy. Exhaustive laboratory workup was unremarkable, but magnetic resonance imaging (MRI) revealed an enhancing pontine mass. The mass was resected, and histopathology revealed a necrotizing granuloma. Although rare, particularly in the pediatric population, the combination of panuveitis and an intracranial mass likely represents sarcoidosis. Necrosis, although also rare, may similarly be seen in neurosarcoidosis.

Key Words: Neurosarcoidosis—Childhood—Uveitis—Intracranial mass—Necrotizing.

Sarcoidosis is an inflammatory disorder of unknown etiology that may involve any organ system. It most commonly affects adults between 20 and 40 years of age. In the United States, the prevalence is >10 times higher among blacks than whites, and women are slightly more susceptible than men (1). The typical presentation follows an insidious onset, with fever, cough, and weight loss being the most common symptoms. Up to 90% of patients show radiologic evidence of pulmonary hilar lymphadenopathy early in the disease course (1,2).

Sarcoidosis in early childhood, however, is a different clinical entity than that in adults, and is characterized by the triad of cutaneous nodules, arthritis, and uveitis (3). Ocular involvement has been reported to approach 100% in these patients (3,4), with iritis and/or anterior vitritis almost universally present. Children >8 years of age have a clinical picture more similar to that of adults. Pediatric sarcoidosis is, itself, relatively rare, with <350 patients <15 of age reported in the literature (5-7).

CASE REPORT

A 13-year-old white boy presented in December 1993 with photophobia and bilateral anterior uveitis, managed with topical steroids. Initial pediatric, neurologic, and rheumatologic evaluations were unrevealing. In March 1994, the patient was asymptomatic with visual acuity of 20/20 in each eye, and normal color vision, visual fields, pupils, and ocular motility. There were 2+ granulomatous keratic precipitates, 3+ cells and flare in the anterior chambers, and 2+ anterior vitreous cells bilaterally. Intraocular pressures were normal. Both optic discs were mildly elevated and hyperemic. In the temporal periphery of each eye, there were a few flat choroidal infiltrates. There were no
signs of retinal vasculitis or snow-banking of the pars plana. Work up at that time included chest radiography, CBC, ESR, ACE, ANA, Lyme titers, HLA B-27, serum calcium, urinalysis, and PPD, all of which were normal.

One month later, he developed binocular vertical diplopia. Visual acuity was 20/20 in each eye and external, slit-lamp, and fundus examinations remained unchanged. Motility examination revealed a flick of right hypertropia in the primary position that increased to 3 prism diopters on left gaze and 4 prism diopters on right head tilt. Double Maddox rod testing revealed 4° of exyclotor-sion, consistent with paresis of the right superior oblique.

Magnetic resonance imaging (MRI) of the brain revealed an enhancing pontomesencephalic lesion that appeared centered at the floor of the fourth ventricle just to the left of the midline and extending bilaterally into the cerebellum (Fig. 1). A second enhancing lesion was seen in the inferior portion of the right internal capsule, and a third zone was identified in the inferior left basal ganglia region (Fig. 2). Early hydrocephalus was present, with prominent temporal horns. There was no enhancement of the leptomeninges, optic nerve, or chiasm; the lacrimal and parotid glands were normal.

A suboccipital craniotomy was performed. At surgery, the tumor was seen to arise from the left side of brainstem, pushing the median raphe toward the right. The mass was completely resected. Cerebrospinal fluid (CSF) taken intraoperatively from the cisterna magna showed normal levels of protein and glucose, and no malignant or inflammatory cells.

Although frozen sections were interpreted as "focally calcified neoplasm consistent with astrocytoma," permanent sections revealed granulomatous inflammation with widespread necrosis, dystrophic calcification, and giant-cell formation (Fig. 3). Special stains for acid-fast bacilli, fungi, and bacteria were negative. Because of the possibility of tuberculosis (TB) infection, the patient was started on a full course of anti-TB medication while waiting for the final cultures. Treatment consisted of isoniazid (INH) 300 mg q.i.d., ethambutol 800 mg q.i.d., rifampin 600 mg q.i.d., pyrazinamide

FIG. 1. A: T1 gadolinium-enhanced sagittal image revealing large ponto-mesencephalic mass (arrows) abutting forth ventricle and midline cerebellum. B: Coronal image shows mass centered left of midline.

FIG. 2. T1 gadolinium-enhanced coronal image reveals bilateral enhancing lesions in the internal capsule/basal ganglia (arrows). Note prominent of temporal horns (arrow heads).
500 mg t.i.d., and vitamin B6 50 mg q.i.d., as well as prednisone 50 mg b.i.d.

All special histological stains were negative, as was gene amplification for DNA of mycobacteria TB (via the polymerase chain reaction). Repeat assays of CSF and blood were performed for bacterial, viral, mycobacterial, and fungal infections, as well as for cysticercosis. ACE and lysozyme levels were normal. The diagnosis of TB was thus ruled out and anti-TB treatment discontinued, together with gradual tapering off of steroids.

Postoperatively, the patient had a transient left internuclear ophthalmoplegia, as well as a peripheral facial nerve paresis and cerebellar ataxia. The fourth cranial nerve paresis persisted, and a contralateral superior oblique paresis became apparent. Repeat, gadolinium-enhanced MRI 3 weeks after surgery was normal.

At 2 months postoperatively, while on prednisone 20 mg every other day, low-grade anterior uveitis remained, but more choroidal nodules appeared in the posterior pole and mid-periphery bilaterally (Fig. 4). In addition, a nodule was present in the right papillomacular bundle, elevating the macula at its temporal border. Visual acuity in the right eye dropped to 20/30. Prednisone was increased to 30 mg/day and the choroidal nodules gradually resolved, with vision returning to 20/20.

FIG. 3. Granulomatous inflammation with area of necrosis (curved arrow), and giant cells (arrow). Hematoxylin-eosin, ×10.

FIG. 4. Left fundus demonstrating multiple choroidal nodules (arrows).
DISCUSSION

Intraocular inflammation can be detected in 20-40% of all adults with sarcoidosis (8). In addition, <10% of all sarcoid patients initially present to an ophthalmologist, while ~7% of patients with persistent uveitis are ultimately diagnosed with sarcoidosis (9,10). Of 59 patients with uveitis found to have systemic sarcoidosis, 23 had involvement of the anterior segment only, 11 had intermediate and/or posterior uveitis, and 25 had panuveitis (10). In another series of patients with sarcoid uveitis, central nervous system (CNS) involvement was absent in all patients who had isolated anterior uveitis, while 11 of 26 patients with posterior or panuveitis had neurological symptoms (11). Brinkman and Rothova (12) similarly described six patients with neurosarcoidosis; all had panuveitis (12).

Sarcoidosis involving the CNS is relatively uncommon, occurring only in 5% of patients with systemic sarcoidosis (1,2). Up to 50% of patients with neurosarcoidosis may present initially with neurologic dysfunction. On the other hand, systemic manifestations of sarcoidosis were found in 97% of patients presenting with neurosarcoidosis, typically at intrathoracic (88%) or ocular (55%) sites (13-15). Nonetheless, a small number of patients who present with neurologic manifestations may have no evidence of extraneural disease (13,15-17). As in adults, CNS involvement in children with sarcoidosis is rare. In a review of 261 cases of pediatric sarcoid, Weinberg (5) found only 11 cases with neurologic involvement (5).

The most common manifestation of neurosarcoidosis is basilar granulomatous meningitis. Accordingly, typical signs and symptoms are those of cranial neuropathies (especially seventh nerve palsies), aseptic meningitis, hydrocephalus, and endocrine disturbances secondary to hypothalamic-hypophysial dysfunction (13-16). Although presentation of neurosarcoidosis as an intracranial mass is rare, diagnostic accuracy of this condition is increasing due to advancements in neuroimaging, and the condition has been recognized in as many as 20% of patients with neurosarcoidosis (16). Cahill and Salcman (13) did a retrospective review of 20 cases (1947-1980), to which they added two of their own cases, of CNS sarcoidosis presenting as a mass lesion. Gizzi et al. (16) found 25 cases (1980-1986) and presented another case. In our review of the literature, we found nine additional cases of neurosarcoidosis presenting as an intracranial, intraparenchymal mass (12,18-21). The youngest patient was 17 years old (21). Masses were most commonly located in the cerebral hemispheres (16,17,21,22), with only a few cases of lesions in the posterior fossa (16,18). In a review of 23 cases of pediatric neurosarcoidosis, only two patients had posterior fossa involvement (5).

It has been suggested that parenchymatous masses in neurosarcoidosis result from extension of the inflammatory process through the spaces of Virchow-Robin (16). Progressive breakdown of pial-glial membranes allows extension of the granuloma into brain parenchyma, and coalescence of these may produce enhancing intra-axial masses identifiable on computed tomography (CT) or MRI. MRI and CT appearances of neurosarcoid mass lesions, however, are nonspecific. On unenhanced scans, sarcoid granulomas have a higher density than brain and show homogeneous moderate-to-high signal enhancement with contrast administration. Unfortunately, meningiomas, metastases, lymphomas, and gliomas may all have a similar appearance (22,23). White matter sarcoid lesions seen on T2-weighted MRI images may resemble those of multiple sclerosis (24).

Histologically, the diagnostic feature of sarcoidosis is the noncaseating granuloma, a compact nodule of epithelial cells with a few lymphocytes, monocytes, and macrophages. Giant cells of either the foreign body or Langhan's type are common. As a rule, necrosis is absent, but even in cases that are clinically typical and from which infection is excluded, eosinophilic necrosis in the center of the lesion has been demonstrated (1).

Necrotizing sarcoid granulomatosis was first described by Liebow in 1973 (25). The clinical manifestations are different from typical sarcoidosis. Almost half of these patients have systemic symptoms, such as fever, sweating, malaise, and weight loss; chest pain is common. Extrapulmonary manifestations are rare, although a few patients are reported with hepatic granulomas and/or uveitis (1). Pathologically, the lesion consists of a collection of epithelioid granulomas in a background of fibrous tissue and nonspecific inflammatory cells. These granulomas are less discrete and less well encapsulated than are those of typical sarcoidosis. Extensive patches of fibrinoid or coagulative necrosis are present, as opposed to the discrete central necrosis seen in TB. This necrosis is probably the result of vasculitis involving both veins and arteries rather than a primary characteristic of the granuloma.

Necrosis has also been reported as a feature of sarcoidosis involving the brain and meninges. Here, it is related to a characteristic periangiitis causing vascular occlusion (26). Of 13 cases of neu-
neurosarcoidosis presenting as a mass lesion, only two cases showed necrotizing granulomatous inflammation (16,21). Additionally, Kelly and Green (27) described a patient with known sarcoidosis who developed optic nerve involvement. Histology of the optic nerve head revealed necrotic foci that were surrounded by granulomatous reaction.

We believe that in the absence of evidence of infection of specific inflammatory process, our patient's clinical course and presentation are consistent with the diagnosis of sarcoidosis. Although atypical by virtue of demography (a 13-year-old white boy), neuroanatomy (multiple intracranial masses), and histopathology (widespread necrosis), all such features have been reported previously. Fortunately, our patient has maintained good visual function, not developing severe and/or bilateral visual loss (28) or requiring cyclosporine (29) or other immunosuppressive therapy. This case underscores the broad spectrum of this entity and is, to our knowledge, the first report of neurosarcoidosis presenting as a necrotizing posterior fossa mass lesion in the pediatric population.


REFERENCES

The One-and-a-Half Syndrome in Systemic Lupus Erythematosus

Aytaç Yiğit, M.D., Ayşe Bingöl, M.D., Nermin Mutluer, M.D., and Nida Taşçilar, M.D.

We report a case of one-and-a-half syndrome occurring as the first manifestation of central nervous system (CNS) involvement in systemic lupus erythematosus (SLE). The lesion in the pons was documented with magnetic resonance imaging (MRI). The patient responded quite satisfactorily to high-dose i.v. methylprednisolone therapy.

Key Words: Systemic lupus erythematosus—One-and-a-half syndrome—Central nervous system involvement—Magnetic resonance imaging.

The "one-and-a-half" syndrome is characterized by the combination of a lateral gaze palsy in one direction with an internuclear ophthalmoplegia (INO) in the other direction. It is usually due to a unilateral lesion in the dorsal pontine tegmentum, involving the ipsilateral paramedian pontine reticular formation, the abducens nucleus, and the internuclear fibers of the medial longitudinal fasciculus. Brainstem infarcts and multiple sclerosis are the most common causes (1).

We report a patient with systemic lupus erythematosus (SLE) who developed a one-and-a-half syndrome as the first manifestation of the central nervous system (CNS) involvement.

CASE REPORT

A 68-year-old woman with a long-standing history of mild SLE presented with acute-onset diplopia and dysarthria, accompanying the activation of discoid rash and photosensitivity.

Neurologic examination revealed a slight right hemiparesis and abnormalities of extraocular movements. In forward gaze, both eyes were in the midline, with no exotropia. On attempted leftward gaze, neither eye moved laterally to pass the midline. On rightward gaze, the left eye did not adduct, but the right eye abducted fully with a lateral nystagmus. Convergence and downward gaze were intact. An upbeat nystagmus occurred on upward gaze. The right hemiparesis resolved spontaneously in 1 day.

Laboratory investigations showed normal values for complete blood counts, erythrocyte sedimentation rate, blood glucose, urea and creatinine, and urinalysis. Serum complement C3c and C4 levels and anticardiolipin antibodies were also within normal limits. Antinuclear antibodies (ANA) were positive (+ + + +), and anti-double stranded
DNA (anti-dsDNA) was 58.0 IU/ml (normal, <7.0 IU/ml). Cerebrospinal fluid analysis was normal.

Cranial T2-weighted magnetic resonance imaging (MRI) revealed a hyperintense lesion in the pons (Fig. 1 left). We treated the patient with methylprednisolone 1 mg/kg/day for 10 days and observed only a slight improvement of extraocular dysfunction (Fig. 2 top). Consequently, we administered intravenous methylprednisolone 1 g/day for the following 3 days. The one-and-a-half syndrome resolved into an incomplete left INO (Fig. 2 bottom). A repeat cranial MRI showed that the pontine lesion was reduced (Fig. 1 right). The oral methylprednisolone at 1 mg/kg/day was continued.

**FIG. 1.** Transverse T2-weighted MRIs showing hyperintense lesion in the pons, extending from the midportion to the left and lower parts. Left: pretreatment, with dimensions of $2 \times 1.5 \times 0.5$ mm. Right: following treatment with high-dose i.v. methylprednisolone, with dimensions of $1.3 \times 0.75 \times 0.4$ mm.

**FIG. 2.** Extraocular movements. Top: one-and-a-half syndrome on day 10 of oral prednisolone. Left, middle, and right photographs are rightward, forward, and leftward gazes, respectively. Note that both eyes pass the midline to the left only slightly on leftward gaze. Bottom: incomplete left internuclear ophthalmoplegia following treatment with high-dose i.v. methylprednisolone. Left, middle, and right photographs are rightward, forward, and leftward gazes, respectively.
for 1 week, without recurrence of the neuroophthalmological signs. The medication was then changed to an alternate-day regimen, dosage tapering in 10 mg decrements every 3 days, and discontinued at the end of 1 month without reactivation of the neuro-ophthalmological signs.

**DISCUSSION**

Our patient presented with a one-and-a-half syndrome characterized by lateral gaze palsy on leftward gaze and INO on rightward gaze. She also fulfilled the American Rheumatism Association criteria for classifying SLE patients (2): positive ANA, anti-dsDNA, discoid rash, and photosensitivity. Neuro-ophthalmological manifestations as INO are rarely associated with SLE. Cogen et al. (3) reviewed six patients with documented unilateral INO in the literature, and described a patient with bilateral INO (3). Another patient with bilateral INO was reported by Jackson et al. (4). To our knowledge, our patient is the first reported case of one-and-a-half syndrome in association with SLE.

Brainstem lesions are infrequently documented in SLE patients (5). In our patient, the T2-weighted MRI showed a hyperintense lesion in the pons that partially resolved following high-dose i.v. steroid therapy. The reduction of one-and-a-half syndrome into incomplete left INO may reflect the resolution of edema surrounding focal ischemia or inflammation (5,6).

In our patient, we obtained the most beneficial effect with high-dose i.v., rather than oral, methylprednisolone administration. This result disagrees with that of Bell et al. (6), who reported that focal CNS manifestations of SLE do not respond to steroid therapy. Although, in some series, brainstem infarcts are associated with high mortality rate (7), patients with only extraocular dysfunction occurring late during mild SLE, may have a more favorable outcome (3,4).

**REFERENCES**

Superficial Siderosis and Episodic Fourth Nerve Paresis
Report of a Case with Clinical and Magnetic Resonance Imaging Findings

Masato Hashimoto, M.D., and William F. Hoyt, M.D.

We describe a patient with superficial siderosis who had an episodic unilateral fourth nerve paresis. The superficial siderosis was caused by small repeated intraventricular hemorrhages from a periventricular cavernous angioma. T2-weighted magnetic resonance images demonstrated a rim of low signal intensity at the brain surface, characteristic of hemosiderin deposition. These low-signal-intensity deposits included the dorsal brain stem around the anterior medullary velum. We suggest that the hemosiderin deposits affected the proximal portion of the fourth nerve where it contains central myelin and that this in some way caused unstable conduction of nerve impulses through the nerve.

Key Words: Superficial siderosis—Hemosiderin—Intermittent diplopia—Magnetic resonance imaging.

Superficial siderosis of the CNS is a chronic condition in which hemosiderin is deposited on the surface layer of the brain, cranial nerves, and spinal cord. After the first neuropathologic description of neuronal and glial changes in superficial siderosis by Noetzel (1) in 1940, it was gradually recognized that superficial siderosis could produce chronic neurologic illness consisting of progressive myelopathy, ataxia, and hearing loss. Once magnetic resonance (MR) imaging became widely available, clinical reports of superficial siderosis increased sharply (2-9). Because of the paramagnetic effect of hemosiderin in T2-weighted images, superficial siderosis produces a strikingly distinctive black rim (of low signal intensity) around the brain and brain stem (10).

To this date no author has suggested that neuro-ophthalmological signs or symptoms should be included among the clinical manifestations of superficial siderosis. We describe episodic diplopia from intermittent trochlear nerve dysfunction in a patient with superficial siderosis confirmed by MR imaging.

CASE REPORT

A 42-year-old woman presented with episodic vertical diplopia. More than 9 years earlier, she had had right-side tinnitus accompanied by headache and leg pain that lasted about 12 days. The pain was precipitated by postural changes from lying to sitting and from sitting to standing. Three years ago, on arising one morning, she had noted that her vision was tilted 45°. When she tried to regain her equilibrium, she lost consciousness for about 30 s. Subsequently, she experienced episodes of severe vertigo and nausea, which re-
solved in 3-4 days. In February 1994, the patient noted the onset of vertical diplopia while hiking. Within 10 min, single binocular vision returned. Since then, episodes of vertical diplopia have gradually increased in frequency.

Neuro-ophthalmologic examination showed visual acuity of 20/20 in each eye. The patient had torsional diplopia when she looked downward to the right and when her head was tilted to the left. These findings were consistent with a variable left fourth nerve paresis.

T2-weighted MR images showed a rim of low signal intensity around the medulla, pons, and midbrain, particularly at the level of the colliculi, presumably caused by hemosiderin deposits (Figs. 1 and 2). The T2 images also showed low signal intensity around the intracanal segments of both optic nerves (Fig. 1). These abnormalities were not apparent on computerized tomography scans or T1-weighted MR images. T1- and T2-weighted MR images also showed a small, round, well-demarcated left-side periventricular mass with mixed signal intensity (Fig. 3), consistent with a cavernous angioma or a cryptic vascular malformation.

**DISCUSSION**

Histologically, superficial siderosis consists of intra- and extracellular hemosiderin deposits in the subpial tissue of the brain and spinal cord and in the ependymal and subependymal lining of the ventricular system. The hemosiderin deposits are thought to be caused by episodic subarachnoid or intraventricular bleeding from capillary or venous sources located anywhere along the cerebrospinal axis. In a review of 40 cases of superficial siderosis...
of the CNS (11), the presumed bleeding source was determined in only 26 cases. The most common causes were brain tumors, especially ependymomas (12-14), followed by hemispherectomy (15), arteriovenous malformations (14), and subdural hematomas (14,15). In our patient, the cause of superficial siderosis was thought to be small, repeated intraventricular hemorrhages from a periventricular cavernous angioma.

After subarachnoid or intraventricular bleeding, most red blood cells in the cerebrospinal fluid undergo lysis and phagocytosis by macrophages originating from reticuloendothelial cells lining the subarachnoid space. Hemoglobin is converted to hemosiderin and then removed from the subarachnoid space. When chronic bleeding occurs, phagocytosis of the constituents of red blood cells may be incomplete, resulting in the deposition of hemosiderin in the CNS. In a histochemical study using a rabbit model of superficial siderosis, Koeppen et al. (14,16) demonstrated that hemosiderin deposits on the surface of the CNS are strongly related to the phagocytosis of microglia of the CNS.

Superficial siderosis selectively involves the surfaces of the cerebellum, brainstem, spinal cord, and the first, second, and eighth cranial nerves. Koeppen et al. (16) proposed that the vulnerability of the cerebellar molecular layer probably relates to the abundance of ferritin-reactive microglia and the presence of Bergmann glia, including ferritin-repressor protein, which accelerates ferritin biosynthesis. The selective vulnerability of the first and second nerves is explained by the fact that their fibers are invested by central myelin and glia. However, there have been only a few reports of superficial siderosis causing olfactory or visual impairments (17-19). Our patient had normal visual function even though T2-weighted MR images demonstrated superficial low signal intensity on both optic nerves. The eighth nerve is believed to be especially susceptible to the effects of hemosiderin because its transitional zone from central to peripheral myelin extends almost to the internal acoustic meatus (20). The transient tilted vision and tinnitus in our patient might have been caused by hemosiderin effects on the subarachnoid segment of the eighth nerve; however, T2-weighted MR imaging showed no obvious deposits in this area.

Anatomically, the fourth nerve nucleus is located at the pontomesencephalic junction at the level of the inferior colliculus, just ventrolateral to the cerebral aqueduct. Its fibers course posteroinferiorly around the aqueduct and decussate within the anterior medullary velum just below the inferior colliculus before they run ventrolaterally around the brainstem in the ambient cistern. Fraher et al. (21) observed histopathologically the transitional zone between central and peripheral myelin in the fourth nerve and noted a distally tapering projection of central myelin extending into the subarachnoid segment of the nerve for a mean distance of 296 ± 76 μm (Fig. 4). Hemosiderin deposits in the fourth nerve would occur at the more central portion of this glial transitional zone. In our patient, MR images demonstrated prominent low signal intensity of the dorsal brainstem surface, including the anterior medullary velum, suggesting dense hemosiderin deposits along the proximal portion of the fourth nerve. We have no explanation for the unilaterality of the episodic variations in our patient's fourth nerve function.

FIG. 4. The transitional zone between central and peripheral myelin in the fourth nerve; T, transitional zone; IV, the fourth nerve; M, dorsal midbrain; D, dorsal; V, ventral; striped, central tissue; shaded, peripheral tissue.
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Dorsal Midbrain Syndrome due to Mesencephalic Hemorrhage
Case Report with Serial Imaging

Andrew G. Lee, M.D., Dennis G. Brown, M.D., and Pedro J. Diaz, M.D.

Spontaneous, nontraumatic, nonhypertensive, midbrain hemorrhage is an uncommon cause of the dorsal midbrain syndrome. We describe a patient with this syndrome in whom the initial neuroimaging studies failed to clearly identify the lesion. Subsequent magnetic resonance imaging studies disclosed a dorsal midbrain hemorrhage. The patient experienced gradual spontaneous resolution of her dorsal midbrain signs and symptoms over several months. The evolution on serial neuroimaging studies of the dorsal midbrain hemorrhage in this patient is described.

Key Words: Dorsal midbrain syndrome—Hemorrhage.

Lesions involving the dorsal midbrain classically present with the neuro-ophthalmologic findings of lid retraction, light-near dissociation of the pupils, upgaze saccadic paresis, and convergence-retraction nystagmus (1-6). Spontaneous, nontraumatic, nonhypertensive, midbrain hemorrhage is an uncommon cause of the dorsal midbrain syndrome (7-11), and the diagnosis is usually confirmed by the initial neuroimaging study. We describe a patient with this syndrome in whom the initial neuroimaging studies failed to clearly identify the lesion; subsequent magnetic resonance (MR) imaging studies revealed a dorsal midbrain hemorrhage. Serial neuroimaging demonstrated evolution of the hemorrhage over time.

CASE REPORT

A 48-year-old normotensive woman with a history of carpal tunnel syndrome and migraine headaches presented on June 26, 1994, with acute binocular oblique diplopia. Neurologic examination by one of us (D.G.B.) revealed a light-near dissociation of the pupils, bilateral lid retraction, bilateral vertical saccadic paresis for upgaze greater than downgaze, mild convergence spasm, convergence-retraction nystagmus on attempted upgaze, and a skew deviation. Oculocephalic testing and forced lid closure (Bell's phenomenon) resulted in improved vertical movement in each eye. The remainder of the neurologic examination was normal.

Computed tomography (CT) scan of the head, blood pressure measurement, echocardiogram, complete blood count, platelet count, and coagulation studies were all normal. MR imaging and MR angiogram of the head were not felt to be diagnostic of a dorsal midbrain lesion (Fig. 1A and
but a single axial T2-weighted MR image was suggestive of a subtle hyperintense focus at the level of the midbrain (Fig. 1C). Lumbar puncture revealed normal protein, glucose, and cell counts, a few oligoclonal bands, and positive myelin basic protein.

Ophthalmological examination on July 12, 1994, by one of us (A.G.L.) revealed a visual acuity of 20/15 OU. The pupils were 6 mm in size OU with a sluggish pupillary light response; there was a brisk near response OU. Slit-lamp examination and ophthalmoscopy were normal. Motility examination was suggestive of a left fourth nerve palsy, but a skew deviation could not be completely excluded. Prism cover testing revealed a left hypertropia of 2 prism dipters at distance; an esotropia of 5 prism dipters at near; an esotropia of 5 prism dipters and a left hypertropia of 5 prism dipters in right gaze; and a left esotropia of 6 prism dipters and a left hypertropia of 2 prism dipters on left gaze. On head tilt to the right, there was a left hypertropia of 5 prism dipters; on head tilt to the left, there was a left hypertropia of 5 prism dipters. There was definite lid retraction in each eye without lid lag in downgaze. Upward saccades were moderately impaired. Convergence–retraction movement in both eyes was elicited on attempted upgaze and on attempted upward saccades in response to the optokinetic (OKN) drum rolling downward. There was a mild defect in downward saccades, but smooth pursuit was intact.

A second MR scan was performed on July 11, 1994; it revealed a definite hyperintense focus on
both T1-weighted and T2-weighted images at the level of the right dorsal midbrain (Fig. 2). Cerebral angiography was not performed.

One week later, neuro-ophthalmological examination showed improved elevation and depression in both eyes; an esotropia of 1 prism diopter and a right hyperphoria of 1 prism diopter; bilateral lid retraction; and light-near dissociation of the pupils. Convergence–retraction nystagmus could not be elicited, and the remainder of the ocular examination was normal.

On November 7, 1994, five months after presentation, T2-weighted coronal and axial MR images (Fig. 3) revealed a hypointense focus in the right dorsal midbrain, which was felt to be related to the presence of hemosiderin and interval hemorrhage evolution. The patient had minimal residual lid retraction, a mild light-near dissociation of the pupils, and a normal motility examination; she was visually asymptomatic.

**DISCUSSION**

The common features of the dorsal midbrain syndrome in our patient included bilateral lid retraction, light-near dissociation of the pupils, up-gaze saccadic paresis, a hyperdeviation possibly due to a fourth nerve palsy or a skew deviation, and a convergence–retraction movement on attempted upgaze. A number of conditions have been reported in association with the dorsal midbrain syndrome, including pineal region neoplasms (1), obstructive hydrocephalus (2), aneurysm (3), and dorsal midbrain infection (1), infarction (4), or demyelination (5).

Although brain stem infarction and thalamic hemorrhage with brain stem involvement have been reported in association with a clinical dorsal midbrain syndrome (4,6), isolated midbrain hemorrhage is an uncommon cause for the syndrome (7–11). Sand et al. (8) reported three cases of non-traumatic, nonhypertensive dorsal midbrain hemorrhages: one patient had a dorsal midbrain syndrome due to a unilateral hemorrhage in the rostral tectal plate; one had a vertical gaze palsy, skew deviation, and a bilateral oculosympathetic paresis due to a unilateral hemorrhage of the superior colliculus, midbrain tegmentum, and rostral dorsal pons; and one had bilateral fourth cranial nerve palsies, a unilateral oculosympathetic paresis, and...
Ataxia due to a hemorrhage in the caudal tectal plate. The neuro-ophtalmologic findings improved in one patient but were unchanged in the other two. All had initial neuroimaging studies consistent with hemorrhage, but none of these cases had abnormal cerebral angiography. Sand et al. postulated that a "cryptogenic" arteriovenous malformation (AVM) was the source of the hemorrhage (8).

Durward et al. reported two cases of mesencephalic hematoma with upgaze paralysis that they felt was due to a brain stem AVM (9). La Torre et al. reported a hematoma of the quadrigeminal plate due to a cryptic AVM associated with impairment of upgaze (10). Weisberg (11) described six cases of normotensive mesencephalic hemorrhages: all six had impaired upgaze and unequal pupils that reacted poorly to light; two had downward ocular deviation; three had ptosis; and one had limited abduction suggesting a "bilateral abducens paresis." Five patients spontaneously improved, and the remaining one improved after insertion of a diversionary shunt (11). McCormick et al. reported six mesencephalic angiomas out of 68 total brain stem angiomas including two AVMs, one cavernous angioma, and three venous angiomas. Twelve of 68 (18%) brainstem angiomas in this series had bled (12). It is not known if our patient had an occult midbrain AVM, and cerebral angiography was not performed.

In 1993, Link et al. reported seven cases of spontaneous midbrain hemorrhage and reviewed 66 additional cases from the literature (13). They reported neuro-ophtalmologic abnormalities in 58 of 66 patients (88%); conjugate upward gaze paresis was present in 33 of these 58 patients (57%). The temporal profile of symptoms in these patients was acute (<24 h) in 65%, subacute (1 day to 1 month) in 24%, and chronic (>1 month) in 11%. The prognosis was good for the majority of the patients. After a mean follow-up period of 9.4 months, 16 patients (24%) were neurologically normal, 35 patients (53%) had minor neurologic deficits, 10 patients (15%) had moderate neurologic deficits, 3 patients (5%) had died, and 2 patients (3%) had no available follow-up information. None of the seven cases reported by Link et al. had delayed neuroimaging findings (13).

Evolving intracranial hemorrhage may be classified as hyperacute (<24 h), acute (1-3 days), early subacute (3-7 days), late subacute (7-14 days), and chronic (>14 days). The MR signal characteristics in each stage are associated with different forms of hemoglobin. In the hyperacute stage, intracellular oxyhemoglobin results in signal characteristics that are isointense to brain on T1-weighted images and slightly hyperintense on T2-weighted images. In the acute stage, intracellular oxyhemoglobin becomes deoxyhemoglobin, and the hemorrhage becomes slightly hypointense on T1-weighted images and very hypointense on T2-weighted images. In the subacute stages, intracellular methemoglobin becomes deoxyhemoglobin, and the hemorrhage becomes slightly hypointense on T1-weighted images and very hypointense on T2-weighted images. In the subacute stages, intra- and extracellular methemoglobin are hyperintense on T1-weighted images. On T2-weighted images, intracellular methemoglobin is very hypointense, and extracellular methemoglobin is hyperintense.

Hemosiderin is the classic finding in chronic hemorrhage and is seen as a hypointense rim on T2-weighted images (14-16). In our patient, the lesion was hyperintense on T1- and T2-weighted im-

FIG. 3. T2-weighted coronal (A) and axial (B) MR images from November 7, 1994, reveal a markedly hypointense focus in the dorsal midbrain on the right, consistent with the presence of hemosiderin related to hematoma evolution (arrows).
ages on July 11, 1994, and was hypointense on T2-weighted images on November 7, 1994, consistent with evolving hemorrhage.

The clinical signs and symptoms of the dorsal midbrain syndrome have specific localizing value, and careful directed neuroimaging studies usually will disclose an etiology. In patients without a definite lesion on initial studies, repeat neuroimaging of the dorsal midbrain may be indicated. The close anatomic relationship of multiple important neurologic structures within the relatively compact dorsal midbrain may account for the presence of pronounced clinical signs even in patients with a small lesion. In addition, a small lesion in the dorsal midbrain may be missed or overlooked on an initial neuroimaging study (13).

We have described serial neuroimaging in a patient with the dorsal midbrain syndrome secondary to a mesencephalic hemorrhage in whom the initial CT and MR scan were not diagnostic. Her symptoms and signs gradually improved without treatment, and serial neuroimaging studies were consistent with evolving hemorrhage.

REFERENCES
Atrophy of Bilateral Extraocular Muscles
CT and Clinical Features of Seven Patients

Kouichirou Okamoto, M.D., Jusuke Ito, M.D.,
Susumu Tokiguchi, M.D., and Tetsuya Furusawa, M.D.

Extraocular muscles consist of four rectus and two oblique muscles. With appropriate techniques, each muscle can be demonstrated on computed tomography (CT) (1,2). Enlarged extraocular muscles encountered in various orbital disorders are also well demonstrated on CT (3,4). However, atrophic extraocular muscles are rarely observed (5-8), and bilateral atrophy is extremely rare (8). We report seven patients with bilateral extraocular muscle atrophy.

MATERIALS AND METHODS
Bilateral extraocular muscle atrophy was noticed in seven patients. We scanned their orbits using 5-mm section axial CT. In addition, we obtained thin-section (1.5- or 2.5-mm thick) axial images and a reformatted coronal image at midorbit for four patients. Spin-echo magnetic resonance (MR) images were available for three patients (nos. 1, 4, and 6).

RESULTS
We divided the patients into two groups: four with mitochondrial myopathy (MM) and three with myasthenia gravis (MG). A diagnosis of MM was confirmed by finding ragged-red fibers on muscle biopsy and by demonstrating a deletion of the mitochondrial DNA. Two patients with complete heart block and pigmentary degeneration of the retina were diagnosed as having Kearns-Sayre syndrome (KSS), and another two as having chronic progressive external ophthalmoplegia. An incorrect diagnosis of MG was initially made in...
TABLE 1. Clinical data of patients with bilateral atrophy of the extracocular muscles

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Initial symptoms</th>
<th>Duration (yr)</th>
<th>Thymectomy</th>
<th>Muscle biopsy</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56 M</td>
<td>Exotropia</td>
<td>-40</td>
<td>+</td>
<td>(RRF+)</td>
<td>CPEO</td>
</tr>
<tr>
<td>2</td>
<td>45 F</td>
<td>Blepharoptosis</td>
<td>21</td>
<td>+</td>
<td>(RRF+)</td>
<td>MG → CPEO</td>
</tr>
<tr>
<td>3</td>
<td>45 F</td>
<td>Blepharoptosis</td>
<td>22</td>
<td>+</td>
<td>(RRF+)</td>
<td>CPEO</td>
</tr>
<tr>
<td>4</td>
<td>44 M</td>
<td>Double vision, ptosis</td>
<td>32</td>
<td>+</td>
<td>(RRF+)</td>
<td>KSS</td>
</tr>
<tr>
<td>5</td>
<td>55 M</td>
<td>Blepharoptosis</td>
<td>41</td>
<td>+ (thymoma)</td>
<td></td>
<td>MG</td>
</tr>
<tr>
<td>6</td>
<td>42 F</td>
<td>Blepharoptosis</td>
<td>22</td>
<td>+</td>
<td>(hyperplasia)</td>
<td>MG</td>
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<td>29 F</td>
<td>Double vision, ptosis</td>
<td>7</td>
<td></td>
<td>(hyperplasia)</td>
<td>MG, hyperthyroidism</td>
</tr>
</tbody>
</table>

Average 46.1

RRF, ragged-red fibers; CPEO, chronic progressive external ophthalmoplegia; MG, myasthenia gravis; KSS, Kearns-Sayre syndrome.

two patients because of mildly positive Tensilon tests. One patient (no. 2) underwent thymectomy 1 year before CT examination and muscle biopsy.

A diagnosis of MG was established because of positive Tensilon testing. Acetylcholine receptor antibody was also positive in one patient (no. 7). In another, (patient 5), the antibody was negative, but the diagnosis was supported electrophysiologically. All patients with MG underwent thymectomy. Histological diagnosis of thymoma was made in one case, and thymus hyperplasia in the other two.

In six of the seven patients, the clinical history suggested a process >20 years in duration. The remaining patient (no. 7) had myasthenic weakness for a duration of 7 years. She was untreated and was found to have hyperthyroidism as well. Eye movement was limited to 5 to 10° in five patients and to 2 to 3° in one (patient 7). The globes were frozen in the other (patient 4). We summarize clinical data in Table 1.

The orbital CT and MR appearances were similar in every patient (Figs. 1, 2). Markedly wasted extracocular muscles with the exception of the inferior oblique muscle were demonstrated bilaterally on a reformatted image (Fig. 1B). We saw no abnormal signal intensity in the atrophic muscles on MR imaging.

DISCUSSION

Each extraocular muscle can be demonstrated and identified on thin-section axial CT scans and on reformatted images (1,2). Enlargement of the muscles encountered in various conditions is well reported (3,4), but a paucity of patients with atrophy have been demonstrated (5-8). Bilateral atrophy is extremely rare and is mentioned in only one case of probable KSS so far (8).

Damage to a motor nerve innervating striated muscle may result in loss of muscle mass (9). However, extraocular muscle mass is normal in most patients with extraocular muscle disease (7,8). In six of our seven patients, the clinical history was >20 years. During this study, we also saw seven other myasthenic patients who had normal extraocular muscles on imaging. The ocular motor deficiencies were milder, and the length of clinical involvement less (Table 2). The shortest reported onset of orbital muscle atrophy is 2 years in a patient with a lateral rectus muscle paresis secondary to a posterior fossa dermoid cyst (6). In our series,
FIG. 2. Patient 7. Thin-section CT image of the orbits in a 29-year-old woman with untreated myasthenia gravis and hyperthyroidism.

the shortest observed onset was 7 years, occurring in a patient with untreated MG.

Prognostically, if muscle atrophy is severe, functional recovery is improbable (7). In our three myasthenic patients with extraocular muscle atrophy, function of the extremity muscles favorably improved with medication after thymectomy. In contrast, the ocular motor impairments responded poorly. One explanation for this dichotomy is that the structure, innervation pattern, and pharmacological properties of skeletal and ocular muscles are extremely different (10).

Clearly, orbital CT and MR appearances cannot help to clinically differentiate between MM and MG. In general, atrophy of the extraocular muscles occurs in later stages of these disorders, while denervation seemingly leads to an earlier onset of atrophy.

TABLE 2. Clinical data of patients without extraocular muscle atrophy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>Duration (yr)</th>
<th>Thymectomy</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>20 M</td>
<td>MG</td>
<td>19</td>
<td>+ (hyperplasia)</td>
</tr>
<tr>
<td>2</td>
<td>20 F</td>
<td>MG</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>77 F</td>
<td>MG</td>
<td>17</td>
<td>+ (hyperplasia)</td>
</tr>
<tr>
<td>4</td>
<td>42 F</td>
<td>MG</td>
<td>9</td>
<td>+ (hyperplasia)</td>
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<td>-</td>
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<td>MG</td>
<td>1</td>
<td>+ (thymoma)</td>
</tr>
<tr>
<td>7</td>
<td>70 F</td>
<td>MG</td>
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<td>+ (thymoma)</td>
</tr>
<tr>
<td>Average</td>
<td>46.4</td>
<td>9.7</td>
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<td></td>
</tr>
</tbody>
</table>

MG, myasthenia gravis.

REFERENCES

Painful Ophthalmoplegia Syndrome Secondary to Metastatic Renal Cell Carcinoma

Thomas J. Mehelas, M.D. and Gregory S. Kosmorsky, D.O.

A healthy 49-year-old Caucasian man was evaluated for persistent headaches and progressive ptosis and ophthalmoplegia.

In June of 1994, he developed a constant right retrobulbar pain that spread into the forehead and temples (at times graded at 10/10 in intensity) as well as photophobia, but without nausea or a stiff neck. He found some relief by lying in a darkroom. There were no previous headaches nor any family history of headaches. He was treated by his primary care physician with Elavil, Calan, and Excedrin without improvement.

His symptoms persisted, and he presented to an emergency room in late July 1994; he was admitted for further evaluation. At that time, he was noted to have a mild horizontal diplopia and partial right blepharoptosis. A computed tomography (CT) scan of the head was done and read as normal as was magnetic resonance imaging (MRI) of the brain (Figs. 1, 2). Cerebral angiography was normal (Fig. 3). Blood studies—complete blood count (CBC), triglycerides, cholesterol, fasting blood sugar (FBS), coagulation studies—were also normal. He was diagnosed as having migraines and treated with subcutaneous Imitrex, intravenous Reglan, and DHE, none of which improved his headaches. The patient was discharged on amitriptyline and cyproheptadine.

In early August 1994, he was sent for a neuro-ophthalmic evaluation that revealed 20/20 vision OD and OS, and 4 mm pupils with no relative afferent pupillary defect. Ocular motility revealed 10% supraduction, 20% intorduction, 0% abduction, and 100% abduction OD, and 100% ductions in all directions OD. Palpebral fissures were 5 mm OD and 15 mm OD. Rodenstock bases 108 were 21 OD and 20 OS. Conjunctivae were normal and there were no orbital cranial bruits. Resistance to globe retropulsion was normal OU. Facial sensation was intact. Biomicroscopy of the anterior segments, funduscropy, and Goldman perimetry (when the right upper lid was elevated) were normal.

The patient was tentatively diagnosed as a presumed Tolosa-Hunt syndrome (pseudotumor) and given high-dose, tapered, oral corticosteroids (100 mg daily) without improvement. Unfortunately, on serial examinations, the right eye visual acuity progressed to no light perception and the patient developed complete ptosis, a "frozen globe" (no ductions), and persistent headaches with his right cornea and face becoming anesthetic over a 3-month period. Repeat MRI and angiograms were read as normal.

A second neuro-ophthalmic examiner interpreted the previous scans as showing a right cavernous sinus enlargement. A repeat high resolution scan concentrating on the cavernous sinus confirmed this suspicion (Fig. 4). High-dose intravenous therapy did not improve his symptoms or signs. A metastatic workup was suggested.

Upon return to his home, CT of the chest and abdomen were performed with the latter showing a large renal cell mass; a biopsy confirmed carcinoma (Fig. 5). He received 6,000 cGy of radiation to the posterior orbit and cavernous sinus with relief of his headache, but no resolution of the motility defects. He has subsequently died of his disease.
FIG. 1. Axial CT scan at the level of the cavernous sinus which revealed no specific pathology.

FIG. 2. Axial T2 weighted image revealing mild enlargement of the right cavernous sinus.

FIG. 3. Lateral internal carotid arterial injection revealing no abnormalities on the right.

FIG. 4. Coronal T2 weighted MRI revealing enlargement of the right cavernous sinus.

FIG. 5. CT scan of abdomen revealing a left renal mass.
Infective Endocarditis—A Photo Essay

Jaya Varadarajan, M.D., and Eric R. Eggenberger, D.O.

Infective endocarditis is a microbial affliction of the heart valves or endocardium. Subacute bacterial endocarditis (SBE) may result from infection with low-virulence organisms such as Streptococcus viridans and Staphylococcus epidermidis, or partially treated infection. We report a case of SBE with neuro-ophthalmologic manifestations. Key Words: Infective endocarditis—Roth spot.

CASE REPORT

A 37-year-old white male developed headaches and partial complex seizures. Seizures were controlled with Tegretol, and T2-weighted magnetic resonance images of the brain demonstrated three high signal lesions without enhancement following gadolinium (Fig. 1). Lumbar puncture revealed protein of 58 mg/dl, glucose of 57 mg/dl, with 500 RBCs and 30 WBCs (95% mononuclear), and negative cultures. Transthoracic echocardiogram and contrast angiogram of the brain were normal.

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FIG. 1. High-signal lesions on T2 weighted magnetic resonance imaging.
FIG. 2. Goldmann perimetry demonstrates a left homonymous visual field defect with additional defects OS at presentation (A), with subsequent improvement (B–D).
FIG. 3. Roth spots at initial presentation (A) that ultimately resolved with antibiotic treatment (B-D).

FIG. 4. Transthoracic echocardiogram demonstrating the valvular vegetation (arrow).
A month later he noted "spots" in the central visual field OU. Goldmann perimetry revealed a small left homonymous scotoma and several additional scotomas (Fig. 2a), while ophthalmoscopy demonstrated Roth spots (Fig. 3a). Laboratory testing revealed erythrocyte sedimentation rate 70 mm/h, WBC 9.9/mm$^3$, and hemoglobin of 11.5 g/dl. Repeat transthoracic echocardiogram revealed valvar vegetation (Fig. 4) and Streptococcus mutans was cultured from the blood. Following a 6-week course of intravenous penicillin, improved visual fields (Figs. 2b–d) and retinal findings (Figs. 3b–d) were documented.

**DISCUSSION**

Clear-centered retinal hemorrhages in SBE were first described by Moritz Roth in 1872 (1). Although Roth spots are primarily associated with SBE and leukemia, they have also been documented with conditions resulting in increased venous pressure (mothers or neonates following complicated labor or delivery, battered children, difficult intubation, AVM with hemorrhage), ischemia (high-altitude anoxia, carbon monoxide poisoning, profound anemia), increased capillary fragility (hypertension or diabetic retinopathy, phlebitis), oral contraceptive intake, viral pneumonia, and kala azar (2–4). The white center in these hemorrhages usually consists of a fibrin plug that forms as a result of platelet adhesion following capillary wall rupture with extrusion of blood into the nerve fiber layer (2,5). In leukemia, the white center may consist of leukemic cells (6).

Neurologic involvement occurs in 29% of SBE and may result from cerebral ischemia, mycotic aneurysm, headaches, seizures, toxic encephalopathy, or meningitis (7). A high index of suspicion is often required to make the diagnosis of SBE. Transesophageal echocardiography has improved detection of valvular vegetations and may be useful when transthoracic echocardiography is normal (8).

**REFERENCES**


Type of Book: This is a general text on strabismus and amblyopia. Its patient-oriented approach makes it concise reading and a good teaching tool. For the pediatric ophthalmologist or for the neuro-ophthalmologist, it will serve as an agreeable review. Each chapter is succinct—no chapter is more than 15 pages. The diagrams and photos incorporated in the book serve to support the text. Each chapter is devoted to concisely summarizing one specific aspect of strabismus or amblyopia.

Scope of Book: The forward of the book states that it is planned as a practical day-to-day guide in the clinical care of patients, designed for the practicing ophthalmologist, resident, or ophthalmic assistant. Its concise nature allows it to serve also for pediatricians or family practice physicians.

Contents: The book has 20 chapters. Each chapter deals with one specific clinical problem. A typical chapter is short and succinctly covers all aspects of clinical significance in the area addressed. The glossary divides terms into 10 separate sections, with definitions that are simple and easily understood.

Strengths: The book is an excellent source of immediate information for the busy clinician. It also serves as a good general instruction text for review. The concise chapters allow the reader to quickly find the subject of interest and to obtain immediate assistance. The book could be viewed as a first-step pediatric ophthalmology consultation for the general ophthalmologist.

Weaknesses: The fault of the book is probably its strength; while it is concise, the ophthalmologist might be looking for a textbook that covers topics in further detail and depth. Moreover, a neuro-ophthalmologist may not be seeking a text that emphasizes strabismus surgery, as this one does. The neurologic aspects of strabismus are not addressed in depth.

Recommended Audience: This text is a good resource for a general ophthalmologist, an ophthalmology resident, an ophthalmic technician, or a general practitioner.

Critical Appraisal: Given the plethora of pediatric ophthalmology textbooks, it is difficult to imagine that another text could be welcomed. However, this book does fulfill a role that has been lacking up to now. For an individual looking for a concise clinical approach to strabismus and amblyopia, this volume is a valuable tool as a practical guide. For those needing further detail in pediatric ophthalmology or in neuro-ophthalmology, other sources need be consulted.

David B. Werner, M.D.
Central Pennsylvania Eye Associates
State College, Pennsylvania
vitreoretinal surgical techniques; these chapters will be less interesting to the neuro-ophthalmologic community.

Strengths: The strength of this book is the quick, comprehensive overview of many of the most important topics and latest developments in clinical retina. There are more than 600 color photographs, many of which are exquisite examples of the disease entities. The chapters draw heavily on the clinical experience of the authors, providing a practical approach to complex disease entities.

Weaknesses: Some of the chapters are more clinically relevant than others. The chapter on new devices for retinal imaging focuses more on scanning laser technology than is necessary for a practical atlas. Because the chapters are short, some of the topics are covered in a cursory manner. For example, central serous chorioretinopathy is only briefly covered as a differential diagnosis of age-related macular degeneration. The neuro-ophthalmologist may desire greater detail in the discussions than are presented here.

Recommended Audience: This atlas serves as an excellent guide for residents, general ophthalmologists, and retina specialists. The neuro-ophthalmologist, too, would find this a useful book to quickly summarize the important details of a retinal disorder or technique.

Critical Appraisal: The goal of this book was to provide an up-to-date, concise, yet informative overview of retinal disorders. The atlas succeeds in this goal. The authors are able to distill the essence of many complex retinal diseases and their practical management in an easy-to-understand fashion.

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University of Iowa
Iowa City, Iowa


Type of Book: For this multi-authored monograph, the editors have assembled an international group of experts to produce 125 chapters on the subject of headache.

Scope of Book: Virtually all aspects of headache are addressed, from history to basic science to clinical management.

Contents: The International Headache Society classification is used throughout, although individual authors are not afraid to point out the limitations of this system in their discussions. As would be expected, migraine receives the lion's share of attention, though there are eight chapters on cluster headaches and many individual chapters that deal with special issues: e.g., headache in children or in the elderly, post-traumatic headache, and headache in the emergency room.

Strengths: The comprehensiveness of this volume makes it a valuable reference, and the use of multinational authorship provides a window for North American readers into the differences in the pharmacological treatment of headache in Europe and elsewhere. The editors have largely succeeded in taming the diversity of using multiple authors by adhering to a set format for each chapter's organization.

Weaknesses: The length and lack of a single perspective makes this book difficult to read cover to cover. Occasionally, statements appear that seem overly dogmatic, for example, "All patients with retinal migraine should be placed on prophylactic anti-migrainous therapy" (p. 425) or "All patients with the clinical diagnosis of migraine with aura should undergo an imaging study" (p. 434). As with any review published in book form, some new observations, such as the recent description of enhancement of the cisternal segment of the third nerve on MRI in ophthalmoplegic migraine, did not make the publishing deadline.

Recommended Audience: This work can serve as a useful resource for any physician or medical student interested in headache.

Critical Appraisal: As a detailed overview of a common and important clinical problem, The Headaches succeeds admirably.

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Worcester, Massachusetts
Retinal Venous Sheathing and the Blood-Retinal Barrier in Multiple Sclerosis. Birch MK, Barbosa S, Blumhardt LD, O'Brien C, Harding SP. Arch Ophthalmol 1996;114:34-9 (Jan). [Correspondence to Dr. M. K. Birch, St. Paul's Eye Unit, Royal Liverpool University Hospital, Prescott Street, Liverpool L7 8XP, England.]

Twenty-three patients with relapsing-remitting, primary-progressive, or secondary-progressive multiple sclerosis were followed for 6 months to assess the blood-retinal barrier. Patients underwent ophthalmic examination, fluorescein angiography, and magnetic resonance imaging monthly. Six patients had retinal venous sheathing with various findings on fluorescein angiography. There was no correlation between ophthalmic retinal features and multiple sclerosis subgrouping, disease course, or magnetic resonance findings.

Fields of Dreamers and Dreamed-up Fields. Functional and Fake Perimetry. Thompson JC, Kosmorsky GS, Ellis BD. Ophthalmology 1996;103:117-25 (Jan). [Reprint requests to Dr. G. S. Kosmorsky, Division of Ophthalmology, Cleveland Clinic Foundation, 1 Clinic Center, A-31, Cleveland, OH 44195-5024.]

Volunteers posed as neuro-ophthalmic patients and were instructed to fake certain visual field defects, which were described to them. As is never surprising, the volunteers who faked visual field defects were very good at fooling both automated perimeters and technicians doing manual perimetry. Additionally, more experienced technicians were easier to fool than inexperienced ones, probably because of the more methodical way in which experienced technicians tested abnormal areas as well as their meant-to-be helpful exhortations, e.g., “you may not see the light but then it will suddenly appear,” when testing for a presumed scotomatous area.

Hypertropia and the Posterior Blowout Fracture. Mechanism and Management. Seiff SR, Good WV. Ophthalmology 1996;103:152-6 (Jan). [Reprint requests to Dr. S. R. Seiff, University of California, San Francisco, Department of Ophthalmology, K301, 10 Kirkham St, San Francisco, CA 94143-0730.]

Ten consecutive patients, each with a blowout fracture and hypertropia on the affected side, make up this report. Presumably, infraduction was “diminished due to changes in the effective origin and insertion of the inferior rectus muscle,” and such patients should be suspected of having a posterior blowout fracture. They may require surgical intervention if motility does not improve in 10-14 days postaccident.


Five patients with one-and-a-half syndrome and facial nerve palsy developed oculopalatal myoclonus. All had either brainstem or pontine hemorrhage, or stroke. The exact mechanism for development of oculopalatal myoclonus in this setting is discussed.

Retinopathy and Optic Neuropathy in Bone Marrow Transplantation for Breast Cancer. Khawly JA, Rubin P, Petros W, Peters WP, Jaffe GJ. Ophthalmology 1996;103:87-95 (Jan). [Reprint requests to Dr. G. J. Jaffe, P.O. Box 3802, Duke University Eye Center, Durham, NC 27710.]

Nine patients with breast cancer had visual symptoms after chemotherapy with carmustine, cisplatin, cyclophosphamide, and autologous bone marrow transplantation. Optic neuropathy and
Retinopathy were found in five patients, retinopathy alone in three patients, and optic neuropathy in only one patient. Retinopathy is generally resolved with good visual return; however, optic neuropathy less often resolved and, in two patients, showed progression after 4 months. Of all the agents, cisplatin was associated with a higher risk of ocular toxicity when these patients were compared to a control group with similar chemotherapy and bone marrow transplantation but without ocular toxicity.

How to Handle the Pressure or Too Much of a Good Thing. Sedwick LA. Comments. Boghen D, Moster M. *Surv Ophthalmol* 1996;40:307-11 (Jan-Feb). [Reprints are not available.]

A case of a 28-year-old woman with pseudotumor cerebri is presented and discussed with emphasis on current medical and surgical treatment strategies.


A 76-year-old lady with progressive diplopia and right eye pain is presented. She had a partial right third nerve palsy with partial pupil involvement and was ultimately found to have a posterior communicating aneurysm on conventional arteriography after magnetic resonance angiography "failed" to identify an aneurysm. A good discussion ensues as to why magnetic resonance angiography failed and points out that, in this case, magnetic resonance image-producing techniques were suboptimal since other projections of the initial magnetic resonance angiogram data demonstrated the lesion. Recommendations are made that one ensure that one's radiologist is aware of both the area in question and lesion suspected when ordering magnetic resonance angiography.

Spasm of the Near Reflex: A Spectrum of Anomalies. Goldstein JH, Schneekloth BB. *Surv Ophthalmol* 1996;40:269-78 (Jan-Feb). [Reprint address: Dr. J. H. Goldstein, Department of Ophthalmology, State University of New York, Health Science Center at Brooklyn, 450 Clarkson Ave—Box #28, Brooklyn, NY 11203.]

This major review deals with this subject in its entirety and serves as a good reference for the clinician who is trying to sort out spasm of accommodation versus spasm of convergence versus spasm of the entire near flex. There is a discussion regarding neuroanatomic correlates and pathophysiology, but the author notes that the clinician is often "perplexed with regard to which patients should be 'worked up'."


A 9-year-old boy had bilateral disc edema and a retinal mass in one eye. He had numerous optic nerve drusen on clinical examination, and the mass proved to be a choroidal neovascular membrane caused by the drusen.

Ocular Signs and Symptoms Caused by Exposure to Sarin Gas. Kato T, Hamanaka T. *Am J Ophthalmol* 1996;121:209-10 (Feb). [Inquiries to Dr. T. Kato, Department of Ophthalmology, Japanese Red Cross Medical Center, 4-1-22 Hiroo, Shibuya-ku, Tokyo, Japan; fax: 81-3-3409-1604.]

Many individuals exposed to sarin gas (a cholinesterase inhibitor) during the Tokyo subway terrorist attacks of March 1995 were found to have miosis and conjunctival injection. Signs and symptoms spontaneously abated in 3-21 days and were not affected by systemic atropine treatment. Ocular pain, however, was relieved with 0.5% tropicamide, presumably for relief of ciliary spasm.

A 35-year-old woman with AIDS presented with mental status change, fever, pneumonia, and lethargy. On examination, she had bilateral vitritis and chorioretinitis. Her workup disclosed tuberculosis with central nervous system, ocular, and pulmonary involvement; she improved on triple-drug therapy.

**Reading-Evoked Visual Dimming.** Manor RS, Yassur Y, Hoyt WF. *Am J Ophthalmol* 1996;121:212-4 (Feb). [Inquiries to Dr. R. S. Manor, Department of Ophthalmology, Beilinson Medical Center, 49100 Petah-Tikva, Israel.]

A fascinating 49-year-old monocular patient noted a five-year history of visual dimming with reading. He was found to have an intracranial tumor in the orbital apex that probably compressed the optic nerve when the eye was in infraduction.


One hundred and twenty patients with Graves' ophthalmopathy were found in the medical diagnostic index of the Mayo Clinic and the Rochester Epidemiology Project for the period 1976-1990. Of these, 89 (74.2%) patients required no treatment or supportive measures only, six (5%) were treated with systemic corticosteroids, one had orbital radiotherapy, and 24 (20%) had one or more surgical procedures (lid, strabismus, and/or orbital decompression). This is reassuring information to give patients with Graves' ophthalmopathy who may ask their chance of needing medical or surgical intervention when seen early in the disease course.

**The Current Use of Botulinum Toxin Therapy in Strabismus.** Rosenbaum AL. *Arch Ophthalmol* 1996;114:213-4 (Feb). [Reprint requests to Dr. A. L. Rosenbaum, Jules Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90024-7001.]

This editorial describes current and possible future indications for the use of botulinum toxin in the treatment of strabismus.

**Ocular Amyloidosis, With Special Reference to the Hereditary Forms With Vitreous Involvement.** Sandgren O. *Surv Ophthalmol* 1995;40:173-96 (Nov-Dec). [Reprint address: Dr. O. Sandgren, Department of Ophthalmology, University of Umeå, S-901 85 Umeå, Sweden.]

This is a major review of the subject with truly lovely color clinical photographs, including pupillary "scalloping." A very nice reference.

**The Relative Afferent Pupillary Defect and a Novel Method of Fusion Recovery With the Worth 4-Dot Test.** Johnson LN. *Arch Ophthalmol* 1996;114:171-5 (Feb). [Reprint requests to Dr. L. N. Johnson, Neuro-ophthalmology Unit, Mason Institute of Ophthalmology, University of Missouri-Columbia, Columbia, MO 65212.]

The author placed neutral density filters in front of the better eye in patients who had a relative afferent pupillary defect and found that Worth 4-dot testing improved to a fusion response with increasing neutral density filters, although tests of stereopsis did not improve. The author suggests that Worth 4-dot neutralization testing "may be a useful adjunct in the assessment of visual dysfunction."


A 39-year-old woman suffered a branch retinal artery occlusion of her right eye, thought to be secondary to migraine or mitral valve prolapse. Her vision recovered to near normal, and, 7 years later, she developed right periorcular discomfort and a third order neuron Horner's syndrome. The discussants conclude that the right carotid artery must be the origin of the pathology; the patient was subsequently found to have a right internal
carotid artery dissection. She did well with anticoagulation.


A patient with Boucher-Neuhauser syndrome (spinocerebellar ataxia, chorioretinal dystrophy, and hypogonadotropic hypogonadism) is described. This syndrome is an autosomal recessive disorder. Only five families with the disorder have been reported, but none in eye literature. This 39-year-old woman complained of decreased vision for 2 years duration and was found to have an atrophic retinal pigment epithelium, choriocapillaris, and clumps of pigment deposition. She had had delayed puberty, medication-induced menses only, and, at age 28 years, started to have balance problems.


Four patients aged 40–73 years presented with ocular motor nerve palsy or palsies, or gaze palsy. Neuro-imaging showed meningeal inflammation and, in one patient, parenchymal disease, but laboratory testing (antineutrophil cytoplasmic antibodies) was initially negative for all patients. This disease is discussed, in general, with attention to its ophthalmic and neurologic complications.


The authors examine patients with neurofibromatosis 2 as well as asymptomatic gene carriers for ophthalmic manifestations of the disease. Cataracts at a young age (67%) and retinal hamartomas (22%) were seen as well as ocular motility nerve palsy (12%) and optic nerve sheath meningioma (2%).


Two patients, aged 37 and 18 years, with insulin-dependent diabetes of unspecified duration developed blurred vision and were found to have bilateral disk edema and decreased acuity in one or both eyes. Intravenous fluorescein angiography was done in each patient. Both had neuro-imaging and cerebrospinal fluid testing. By 10 weeks after onset of symptoms, each patient had optic disc neovascularization and complications from same. The authors caution that these patients should be followed even after initial resolution of symptoms and disc edema.


The authors used normal subjects and a computerized binocular infrared video pupillometer, and varied light stimulus in intensity, duration, and number to determine its effect on the variability of detecting a relative afferent pupillary defect (induced in these subjects by dimming the light stimulus to one eye and later to the other). They found that the variability in measurements decreased with repetitive stimulus tests and that at 100 stimulus pairs, the 95% confidence level was <0.1 log unit. Although they propose that such testing will have clinical effectiveness, it is hard to see how a several-min-long test of pupillary function with very sophisticated equipment will ever be cost-effective in the community.
Vasospasm—A Risk Factor for Nonarteritic Anterior Ischemic Optic Neuropathy? Kaiser HJ, Flammer J, Messerli J. Neuro-ophthalmology 1996;16: 5-10 (February). [Reprint requests to Dr. J. Flammer, University Eye Clinic, P.O. Box CH-4012 Basel, Switzerland.]

Nonarteritic anterior ischemic optic neuropathy (AION) is a disease of elderly patients with known risk factors such as disc at risk and cardiovascular disease. This paper reports five patients aged 12 to 44 with AION (swelling of the optic disc, loss of central vision, visual field defect). All patients are reported to have capillary spasm detected with fingernail capillary-microscopy. Treatment consisted of the administration of a calcium antagonist, dipyridamole, beta blockers, or mineralocorticoids. Visual acuity and visual field improved drastically in all patients. This paper raises interesting questions concerning a possible relationship between vasospasm and AION. The main question, however, is whether these patients represent a homogeneous group—the “normal” laboratory parameters are not specifically listed.


Temporal artery biopsy is the golden standard to diagnose temporal arteritis. To move away from invasive diagnostics, the authors performed color Doppler sonography in 10 patients with temporal arteritis, 8 patients with polymyalgia rheumatica, and 23 controls. The parameters measured the size of the lumen and wall as well as blood flow velocity. Color Doppler sonography of the superficial temporal artery showed a characteristic hypoechoic halo around the perfused lumen of a stenosed or occluded artery. Neither patients with polymyalgia rheumatica nor controls showed this hypoechoic halo, which disappeared 10 to 14 days after glucocorticoid treatment. The authors conclude that color Doppler sonography is a simple, quick, and noninvasive method to diagnose temporal arteritis.

Fourth Nerve Palsy in Migraine. Wong AMF, Sharpe JA. Neuro-ophthalmology 1996;16: 51-4. [Reprint requests to Dr. J. A. Sharpe, Division of Neurology, The Toronto Hospital, EC 5-042, 399 Bathurst Street, Toronto, Ontario Canada M5T 2S8.]

Transient third nerve palsy in children due to migraine is a well-known entity called ophthalmoplegic migraine. A 15-year-old Caucasian boy presented with recurrent oblique diplopia. He had a 7-year history of common migraine. Since age 13, each migraine attack had been associated with oblique diplopia that increased in downgaze. Physical examination, cranial CT and MRI studies, and magnetic resonance angiography (MRA), as well as laboratory work-up, were normal. Administration of Fiorinal, propranolol, Calergot, and sumatriptan failed to prevent the headaches as well as the diplopia. The authors suggest that recurrent fourth nerve palsy associated with migraine may be included in the differential diagnosis of fourth nerve palsy.
Letter to the Editor

Predominant Downgaze Ophthalmoparesis in Anti-Hu Encephalomyelitis

To the Editor:

In a recent article, Crino et al. (1) reported the cases of three patients with paraneoplastic brain-stem encephalitis and ophthalmoparesis, two of them associated with the presence of anti-Hu antibodies in the serum. We report another case of paraneoplastic anti-Hu-associated encephalopathy with midbrain signs and predominant downgaze paresis. An active 62-year-old woman experienced difficulty in reading and walking downstairs together with daytime sleepiness, episodes of slurred speech, staring, and unresponsiveness, which worsened over several weeks. Her medical and family histories were unremarkable except for a 35-pack-year history of cigarette smoking with no complaints of headaches, double vision, gastrointestinal problems, rheumatologic symptoms, insect bites, diabetes mellitus, or hypertension. When alert and cooperative, she was oriented to time and intermittently to place, but her short- and long-term memory were impaired. She made errors in calculation, and her speech was dysarthric. She was hypersomnolent, and within moments she would lapse into inattention and mutism, during which time she followed no directions and was unable to stand up or walk. A grasp reflex was present, but startle myoclonus was absent. Upper-extremity tone was mildly increased without axial rigidity; trace left-upper-extremity dysdiadochokinesis was noted, and ankle jerks were absent. Her visual acuity was 20/20 for individual letters, but she was unable to read. Her visual fields were intact, and her pupils reacted sluggishly to light but without relative afferent defects. Fixation was interrupted by square-wave jerks. No vertical OKN could be elicited, and horizontal OKN was poorly formed. On attempted downgaze, the patient moved her chin downward, and paradoxically rolled her eyes up. On attempted upgaze, the palpebral fissure widened, with an occasional beat of convergence retraction nystagmus. No other nystagmus or rhythmic movements of the mouth or palate were observed. Horizontal pursuit was jerky with slowed hypometric saccades. Bilateral ptosis was present, which did not improve with rest.

Blood tests, including a complete blood count with smear, chemistries, coagulation profile, TFTs, acetylcholine receptor antibody, antinuclear antibody, WESR, VDRL, and Lyme titer, showed normal results. Magnetic resonance imaging and angiography, transesophageal echocardiography, carotid duplex scan, cerebral angiography, pelvic/abdominal computed tomography (CT), and jejunal biopsy also gave normal results. Repeated spinal taps showed elevated white cells (9–20/mm³) with normal glucose and protein levels and negative cytology. A 24-h continuous EEG showed results that had no correlation with behavioral disturbances, and during an Amytal interview the patient was more organized, without lapses in contact but with no improvement in memory, calculation, speech, or eye movements. A temporal lobe biopsy showed no evidence of Creutzfeldt-Jacob disease, lymphoma or periodic-acid-Schiff-positive macrophages. A brief therapeutic trial of steroids yielded no improvement. A 2-week course of intravenous ceftriaxone as empiric treatment for Whipple’s disease was not effective. A screen for paraneoplastic antibodies in the patient’s cerebrospinal fluid (CSF) and serum found high titers of anti-Hu antibodies. Subsequent CT scan of the chest showed two enlarged mediastinal lymph nodes, which on CT-guided biopsy proved to be invaded by small-cell carcinoma of the lung.

Anti-Hu antibodies in CSF or serum are diagnostic of a paraneoplastic syndrome most frequently associated with small-cell carcinoma of the lung (2,3). Women are affected more commonly than men. Often the diagnosis of malignancy is not made until after the onset of neurologic symptoms. Multifocal neurologic symptoms are found in 75% of anti-Hu-positive patients, resulting in sensory neuropathy, limbic encephalitis, cerebellar degeneration, motor neuropathy, autonomic dysfunction, visual loss, and brain-stem encephalitis. Paraneoplastic brain-stem encephalitis may mimic a variety of syndromes, including focal lesions of the midbrain, pons, or medulla. The differential diagnosis in this case consisted of Whipple’s disease, primary central nervous system lymphoma, Creutzfeldt-Jakob disease, and small-cell carcinoma of the lung.
disease, and progressive supranuclear palsy. The patient’s clinical features of vertical gaze paresis with absent downgaze, poor fixation, and hypometric horizontal saccades were suggestive of progressive supranuclear palsy; however, the lack of axial rigidity together with the subacute temporal course of the symptoms was atypical. While many patients with anti-Hu syndrome have had eye movement abnormalities reflecting midbrain pathology, predominance of downgaze paresis has not previously been described.

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