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Orbital Malignant Peripheral Nerve Sheath Tumors
Treatment with Surgical Resection and Radiation Therapy

Sergul A. Erzurum, M.D., Onur Melen, M.D., Gary Lissner, M.D., Deborah I. Friedman, M.D., Alfredo Sadun, M.D., Steven E. Feldt, M.D., and Narsing A. Rao, M.D.

A series of three patients with primary orbital malignant peripheral nerve sheath tumors (MPNST) is presented. Two of our patients who were treated with surgery and postoperative radiation therapy are free of tumor recurrence. The third patient showed a good response to radiation therapy. While surgical excision remains the mainstay of therapy, our patients demonstrate the usefulness of adjuvant radiation therapy in this condition.

Key Words: Surgical resection—Postoperative irradiation—Malignant nerve sheath tumors.

Benign tumors originating from the sheaths of cranial nerves constitute 4% of all orbital tumors (1–3). These tumors are comprised of either solitary schwannomas and neurofibromas or plexiform neurofibromas associated with von Recklinghausen’s disease. Most of these tumors originate from the first division of the trigeminal nerve. They are generally slow-growing tumors with low morbidity. In contrast, malignant peripheral nerve sheath tumors (MPNST) are rare in occurrence. They run an aggressive course with a tendency to recur after surgical resection. These tumors may invade intracranial structures, metastasize to distant sites, and lead to death (4–6). In this report, we describe three such cases of MPNSTs, which demonstrated a response to surgical excision and postoperative irradiation.

CASE REPORTS

Case 1

A 29-year-old man presented in March 1984 with a 7-month history of progressive proptosis and fullness of the right eye. His past medical history and review of systems were negative for neurofibromatosis. Visual acuity was 20/20 in both eyes. Hertel exophthalmometry readings revealed 5 mm of proptosis on the right. The extraocular movements were full, and there was decreased retropulsion of the right globe. The fundus examination was normal.

Computed tomography (CT) scan of the orbits in March 1984 showed a well-circumscribed mass occupying the medial portion of the right orbit. The
mass appeared to be extraconal with bowing of the adjacent orbital wall without any bony destruction. Orbital echography was suggestive of a cavernous hemangioma, and a benign process was suspected.

CT scan in September 1984 showed lateral displacement of the right medial rectus and optic nerve (Fig. 1). The patient requested that the mass be observed with interval CT scans until October 1985 when he developed diplopia on up gaze. The patient consented to a right frontal craniotomy approach to the superior orbit for resection of the tumor. The tumor was located superonasally in the orbit displacing the superior oblique muscle upward, and appeared to originate from the supraorbital nerve. Although most surfaces of the tumor appeared encapsulated, tumor-free margins could not be guaranteed. Histopathological examination demonstrated a cellular spindle cell tumor with variations in cellular density from field to field. Occasional mitoses were seen (Fig. 2). Electron microscopy demonstrated neoplastic cells with long nontapered cytoplasmic ends; however, no well-defined pericellular basement membrane was seen. Immunohistochemistry demonstrated S-100 positivity. In order to exclude malignant melanoma, additional stains for melanin were performed and found to be negative. The Armed Forces Institute of Pathology reviewed the slides and confirmed our diagnosis.

Postoperatively, the patient received a total of 6,000 cGy (centigray) to the entire orbit. Following therapy, the visual acuity remained 20/20 in both eyes, and Hertel exophthalmometry readings revealed 1.5 mm of proptosis on the right. There was mild resistance to retropulsion and minimal restriction of motility. The patient maintained useful vision for 4 years before developing radiation-
induced proliferative retinopathy. The patient has remained free of tumor for 6 years by clinical examination and MRI studies.

Case 2

A 77-year-old man was evaluated in September 1987 for diplopia, right upper eyelid ptosis, and right lower eyelid numbness. In 1985, a right orbital tumor had been discovered at another institution. At that time, the patient had presented with persistent pain in the region of the medial canthus of the right eye. The tumor was surgically removed from the right supranasal area of the orbit, but required a second resection 2 years later because of recurrence. The orbit was subsequently irradiated with a total dose of 6,000 cGy. The histopathologic diagnosis was a highly malignant mesenchymal neoplasm originating from the peripheral nerve bundles, consistent with MPNST.

![Photomicrograph demonstrating markedly cellular tumor with fascicular pattern. Atypical cells with spindle shaped hyperchromatic nuclei are seen. (Hematoxylin and eosin; ×100.)](image1)

![High power view illustrating tumor cells arranged in thin bundles resembling nerve trunks. The nuclei range in size from small to large. Mitotic figures are seen. (Hematoxylin and eosin; ×400.)](image2)
FIG. 4. MR imaging demonstrates posterior extension of the tumor along the course of the trigeminal nerve (arrows).

(Fig. 3). The Memorial Sloane-Kettering Cancer Center reviewed the slides and confirmed the diagnosis.

In September 1987, the patient was admitted to the hospital for evaluation of dysphagia due to esophageal carcinoma and underwent an esophagogastrectomy.

In October 1987, neuro-ophthalmologic consultation was obtained when the patient developed diplopia. His past medical history and review of systems disclosed no evidence of neurofibromatosis. Examination revealed best corrected visual acuity of 20/50 in the right eye and 20/40 in the left eye. Pupillary functions were normal. Complete ptosis and external ophthalmoplegia were present on the right side. The right corneal reflex was lost, and cutaneous sensation over the right forehead and lower lid were diminished. Visual fields and ophthalmoscopy were unremarkable. CT scan demonstrated a mass within the cavernous sinus extending within the orbital apex and supraorbital fissure. Magnetic resonance imaging (MRI) revealed posterior extension of the tumor along the course of the fifth cranial nerve to Meckel's cave (Fig. 4). In addition, T2-weighted images revealed bright signal intensity within the right lateral pons extending toward the fourth ventricular surface. This corresponded to the course of the fifth nerve through the brainstem toward its motor nucleus.

It was decided to treat the tumor extension with irradiation in the hope of slowing the progression. The patient received 1,980 cGy to the cavernous sinus area and an additional 3,600 cGy to the orbit. One week after completion of radiotherapy, the patient was left with a lateral rectus paralysis and 30 prism diopters of esotropia. However, the patient succumbed to the carcinoma of the esophagus and died about a month later. A postmortem examination was not granted.

Case 3

A 58-year-old woman experienced numbness and pain in her right nostril, which extended to her right upper lip in early 1986. Her past medical history and review of systems disclosed no evidence of neurofibromatosis. In March 1987, examination disclosed hypesthesia along the right side of the nose, lip, and malar region.

CT scan of the head, orbits, and sinuses showed a subtle thickening in the inferior mid- to anterior portion of the right orbit. There was a slight inferior convexity of the curvature of the floor of the orbit with mild bone thickening. MRI of the brain was normal.

The pain in the right malar region resolved with prednisone therapy (60 mg daily), only to return in January 1988.

In September 1988, clinical evaluation was unchanged and the MRI demonstrated a well-delineated mass in the inferior orbit. Repeat CT scan showed interval enlargement of the mass, expanding the bony margins of the infraorbital canal, and extending posteriorly through the inferior or-

FIG. 5. CT scan demonstrating interval enlargement of the orbital mass, with bony remodeling inferiorly (arrow).
bital fissure (Fig. 5). A tumor originating from the maxillary division of the trigeminal nerve was suspected.

An inferior orbitotomy in November 1988 disclosed a fusiform, rubbery mass, encased in the orbital floor. The diameter of the mass decreased to conform with the infraorbital canal. The mass was dissected and severed, but the proximal ends contained malignant cells on frozen section. The tumor was removed up to its entry into the sphenoid bone. The remaining posterior tumor mass was removed at craniotomy in December. Minimal anterior extension was removed during concurrent exploration by an otolaryngologist.

Pathological examination showed MPNST arising from the maxillary division of the trigeminal nerve (Fig. 6). Immunohistochemistry demonstrated vimentin and S-100 positivity, but no keratin staining.

Postoperatively, the patient received a total of 5,950 cGy to the entire orbit. The irradiation resulted in marked limitation of jaw mobility, dry

**FIG. 6.** (A) Low power photomicrograph demonstrating the cellular spindle-cell character of the neoplasm. Fascicular pattern is apparent. (Hemotoxylin and eosin; ×40.) (B) High-power view illustrating cells with plump, pleomorphic nuclei comprising the tumor. (Hemotoxylin and eosin; ×400.)
S. A. ERZURUM ET AL.

TABLE 1. Review of orbital MPNSTs in the literature

<table>
<thead>
<tr>
<th>Nerve of origin</th>
<th>Surgical treatment</th>
<th>Metastases or tumor extension</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraorbital (13)</td>
<td>Local excision (12)</td>
<td>Extension to CNS/sinuses (9)</td>
<td>Death related to MPNST (10)</td>
</tr>
<tr>
<td>Infraorbital (3)</td>
<td>Craniotomy (7)</td>
<td>Lungs (4)</td>
<td>Alive &gt;3 yrs (4)</td>
</tr>
<tr>
<td>Intraconal (1)</td>
<td>Orbitotomy (5)</td>
<td>Mediastinum (1)</td>
<td>Inadequate follow-up (4)</td>
</tr>
<tr>
<td>Ophthalmic division (1)</td>
<td>Exenteration (5)</td>
<td>Liver (1)</td>
<td>Unrelated deaths (2)</td>
</tr>
</tbody>
</table>

Number of cases in parentheses. Total number of cases reviewed was 20. The patients developed an average of 1.4 recurrences (range of 0 to 5). Thirteen patients received radiation therapy and two patients received chemotherapy.

*When information was inadequate, those patients were not included in the tabulations.

b More than one procedure was performed on some patients.

eye, and mild infraduction weakness. The patient maintained useful vision until April 1990, when she developed ischemic optic neuropathy. There has been no evidence of tumor recurrence for 3½ years.

DISCUSSION

Only 17 well-documented orbital malignant peripheral nerve sheath tumors (MPNST) have been reported so far in the ophthalmic literature (2,4,5,7–9). Jakobiec and Font (4) published the largest series and provided a comprehensive review of the pathologic and clinical features of these neoplasms. Objective means for identification of MPNST have been attempted by immunohistochemical studies. Series of spindle cell sarcomas have been studied to see if they could be distinguished by immunoreactivity alone. Results have shown that myelin basic protein (MBP), Leu-7, and anti-neuron specific enolase (NSE) are not representative markers of schwannian differentiation. Anti-glial fibrillary acidic protein (GFAP) is rarely expressed but may indicate schwannian differentiation. MPNSTs and leiomyosarcomas seem to share immunoreactivity for 5-100, Leu-7, NSE, and actin. Thus, these two tumors cannot be differentiated on this basis alone (10).

The majority of tumors in Jakobiec and Font’s (4) series were located superonasally in the orbit, indicative of its origin from the supraorbital nerve. Presenting features included subcutaneous nodule near the medial canthus, pain, proptosis, and diplopia. Despite their initial benign appearance, the tumors showed a tendency to grow posteriorly along the supraorbital nerve, extended into the region of the cavernous sinus, and progressed as far as the nucleus of the trigeminal nerve in the pons. Local recurrences were frequent despite surgical resection, and some patients suffered from metastases to regional lymph nodes, mediastinum, and lung. Two of their patients responded favorably to adjuvant radiotherapy and/or chemotherapy once recurrence was detected.

Recently Lyons et al. (5) reported three additional cases of orbital MPNST. These patients presented with eye pain, redness, proptosis, and/or subcutaneous nodule near the medial canthus. All of them suffered from either extensive intracranial extension of the tumor or multiple local recurrences despite surgical excision. None of their patients received radiotherapy. One patient died of his disease, and the other two only had short-term follow-up. The authors recommended extensive surgical resection and exenteration as treatment of choice.

Clinical presentation of our patients were similar to those reported in the literature (Table 1). None of them had systemic neurofibromatosis. Cases 1 and 3 were treated with surgical resection and postoperative irradiation. These patients have remained free of tumor recurrence for 6 and 3 years, respectively; however, they developed proliferative retinopathy and ischemic optic neuropathy, presumably a result of radiotherapy. Our case 2 experienced a local recurrence 2 years after the initial surgical removal. The recurrent tumor was then excised, and the orbit was irradiated. Unfortunately, he presented with cavernous sinus syndrome several months later. Additional irradiation to the posterior orbit and skull base resulted in partial resolution of ophthalmoplegia.

Since these tumors have an aggressive growth pattern and potential for distant metastasis, an attempt should be made to remove these tumors totally within the orbit. If there is intracranial extension, consideration should be given to resect the tumor up to the cavernous sinus. Our limited experience with postoperative radiotherapy suggests its usefulness in prevention of local recurrence up to 6 years. This mode of treatment should be considered as an alternative to exenteration.
REFERENCES

Sudden Visual Field Constriction Associated with Optic Disc Drusen

Tamela A. Moody, M.D., Alexander R. Irvine, M.D., Peter H. Cahn, M.D., John O. Susac, M.D., and Jonathan C. Horton, M.D., Ph.D.

We report two patients with optic disc drusen who suffered sudden, concentric constriction of the visual field. Visual acuity remained normal. The involved discs showed no swelling, hemorrhage, or other evidence of anterior ischemic optic neuropathy. We are unable to explain the mechanism or the pattern of visual field loss in these unusual cases.

Key Words: Optic disc drusen—Visual field constriction—Anterior ischemic optic neuropathy.

Although most patients with optic disc drusen are asymptomatic, defects in the field of vision can usually be evinced upon careful testing. In his classic monograph, Lorentzen (1) reported visual field changes in 87% of patients tested with the Goldmann perimeter. In a later study, Savino, Glaser, and Rosenberg (2) detected visual field loss in 71% of patients with visible drusen. The most common findings were nerve fiber bundle defects, generalized field constriction, and enlargement of the blind spot.

Visual field defects develop insidiously in the majority of patients with optic disc drusen. However, visual field loss may occur abruptly. Most authors have invoked anterior ischemic optic neuropathy to explain the phenomenon of sudden visual loss in patients with optic disc drusen. We describe two patients with optic disc drusen who experienced severe and sudden constriction of the visual field with preservation of normal visual acuity. The diagnosis of anterior ischemic optic neuropathy was tenable in neither patient.

CASE REPORTS

Case 1

An 18-year-old woman was noted on routine examination to have drusen of the left optic disc. Over the following decade, the drusen gradually became more prominent. At age 29, drusen also became evident in the right optic disc. Although the patient was asymptomatic, at age 31 she was tested with a Cooper Vision Auto-Perimeter 120 point screening program. The visual fields were normal, except for 12 points in the left eye missed along an inferior arcuate course. At age 35 the visual acuity was 20/20 OU, the visual fields were unchanged, and the patient remained without symptoms. Fundus photos were taken for the pa-
SUDDEN FIELD CONSTRICTION

FIG. 1. Fundus photograph of the left eye in Case 1 taken on Feb. 19, 1989, 19 months prior to abrupt onset of visual field constriction. The disc appears choked with drusen.

FIG. 2. Visual field of the left eye in Case 1 tested using the 30-2 threshold program of the Humphrey field analyzer. The field shows severe, concentric constriction, but the macular thresholds are normal.

The patient to share with future ophthalmologists who might be worried by the appearance of the optic discs (Fig. 1).

Less than two years later, at age 37, the patient reported that the vision in her left eye suddenly became blurry and dim upon arising from an office chair. On examination 2 days later, the visual acuity was 20/20 in both eyes. The Hardy-Rand-Rittler color plates were all identified correctly with each eye. A left afferent pupil defect was present. The visual fields were tested with a 30-2 threshold program using a Humphrey field analyzer. The visual field of the right eye was normal. The visual field of the left eye showed severe, concentric constriction with preservation of normal central retinal sensitivity (Fig. 2). The foveal threshold was 36 dB in each eye. The retina of the left eye was normal. The optic disc contained innumerable exposed and buried drusen, but no swelling or hemorrhage was evident (Fig. 3). Allowing for variation in photographic technique, we could see no difference in the appearance of the optic disc compared with the photograph taken 2 years earlier, which the patient carried in her purse (Fig. 1). A fluorescein angiogram showed normal perfusion of the left optic disc and retina (Fig. 4). The only abnormal feature was slow leakage from the left optic disc, which resulted in marked hyperfluorescence in late stages of the angiogram (Fig. 5). The patient received a brief course of prednisone, without benefit.

On examination a year later, the visual acuity was 20/20 in both eyes and the Hardy-Rand-Rittler color plates were again identified correctly with each eye. A left afferent pupil defect was still present. Visual field testing of the left eye showed a foveal sensitivity of 38 dB and slight improvement of the visual field. The left optic disc appeared identical (Fig. 6) to the photograph taken the year before. The nerve fiber layer, except for the papillomacular bundle, appeared severely atrophic. A fluorescein angiogram showed late staining of drusen within the optic disc (Fig. 7), but the striking hyperfluorescence noted previously (Fig. 5) was absent.
Case 2

A 37-year-old woman was reported to have drusen in the right optic disc. At age 40, an ophthalmologist noted the presence of drusen in both optic discs. The visual acuity was 20/20 OU and the visual fields were normal when tested with a 3-mm white pin at a distance of 1 m from a tangent screen. The patient remained entirely free of symptoms until a year later, when she noted the sudden appearance of a “film” over the right eye. On examination the visual acuity was 20/20 in both eyes. An afferent pupil defect was present in the right eye. Upon testing at the tangent screen the visual field of the left eye was normal, but the visual field of the right eye showed concentric constriction that spared only the central 5–10°. Both optic discs contained drusen. The right optic disc appeared pale, but no hemorrhage or edema was present. A sedimentation rate, VDRL, carotid angiogram, and pneumoencephalogram were normal. The patient received prednisone, but the visual fields did not improve.

On subsequent examinations the patient reported no further change in the vision in the right eye. When retested 16 years later, at age 56, the visual fields were normal.

FIG. 3. Fundus photograph of the left eye in Case 1 taken on Sept. 20, 1990, 2 days after acute episode of visual loss. The contrast, perspective, and plane of focus vary slightly from Fig. 1. Apart from these differences in photographic technique, there is no change in the appearance of the optic disc.

FIG. 4. Late arterial phase (11.2 seconds) fluorescein angiogram of left optic disc in Case 1 performed on Sept. 20, 1990, demonstrating normal perfusion of the optic disc.
vision was still 20/20 in both eyes. The visual field of the right eye showed severe concentric constriction, sparing only 5° toward the temporal side of fixation (Fig. 8). The foveal sensitivity was 33 dB. The right optic disc appeared pale and filled with drusen. The nerve fiber layer was absent, except for the papillomacular bundle.

**DISCUSSION**

Previous investigators have noted a poor correlation between the location of drusen in the optic disc and the pattern of scotomata in the visual field (1-4). This lack of correspondence argues against mechanical compression or erosion of nerve fibers as a simple explanation for the visual field defects associated with optic disc drusen. It is conceivable, though, that buried drusen unseen with the ophthalmoscope might correlate better with the pattern of visual field loss. Spencer (5) has proposed that a defect in axoplasmic transport at the optic disc is the cause of drusen formation. According to his view, impaired axoplasmic transport leads to axonal death, calcium deposition, and the appearance of drusen within the optic disc. Tso (6) favors a similar mechanism, although he believes a dis-

**FIG. 5.** Later stage (388.9 seconds) of fluorescein angiogram in Case 1 showing hyperfluorescence of the left optic disc.

**FIG. 6.** Follow-up fundus photograph taken Aug. 27, 1991 in Case 1 showing no change in the appearance of the left optic disc, except for loss of the nerve fiber layer outside the papillomacular bundle, which cannot be appreciated on these photographs.
order of axonal metabolism, rather than axonal transport, is responsible for the accumulation of disc drusen. This debate—whether drusen are the cause, or merely a conspicuous by-product, of axonal degeneration—underscores the fact that the mechanism of visual loss in patients with optic disc drusen is still a mystery.

Infrequently, vision loss occurs suddenly in patients with optic disc drusen. The mechanism is unknown. Anterior ischemic optic neuropathy has been offered as an explanation (7-11). Sudden vision loss from disc drusen is usually painless, non-progressive, and may be accompanied by disc edema and hemorrhage. Fluorescein angiography has documented hypoperfusion of the optic disc (8). These features are all characteristic of anterior ischemic optic neuropathy. Moreover, optic discs that contain drusen are usually small, crowded, and lack a physiological cup. Absence of a physiological cup is linked to an increased risk of anterior ischemic optic neuropathy (12-14).

Although anterior ischemic optic neuropathy may provide a satisfactory explanation for the occurrence of sudden vision loss in some patients with optic disc drusen, this diagnosis is difficult to reconcile with the findings in our patients. When examined soon after acute loss of visual field, neither patient had hemorrhage or edema of the optic disc. The diagnosis of anterior ischemic optic neuropathy requires ophthalmoscopic signs of optic disc ischemia. Fortuitously, disc photos were taken in the first patient 2 years before vision loss (Fig. 1). Using these photos for comparison, we could detect no change in the appearance of the optic disc after acute vision loss (Fig. 3). Moreover, 1 year later (Fig. 6), we observed no attenuation of the retinal arteriolar circulation. This sign typically appears as a late sequela of anterior ischemic optic neuropathy (15).

In our first patient, the fluorescein angiogram failed to show hypoperfusion of the optic disc. In a fluorescein study, Karel and coworkers (16) found no filling defects in the disc circulation in patients with sudden visual loss and disc drusen. These
findings neither support nor refute the diagnosis of anterior ischemic optic neuropathy, inasmuch as Kommerell and coworkers (17) have obtained normal fluorescein angiograms of the optic disc circulation in patients with anterior ischemic optic neuropathy.

In our patients, the most striking feature of the drusen-associated visual loss was the sudden and severe loss of peripheral vision with preservation of normal visual acuity. This pattern of concentric visual field constriction is not consistent with anterior ischemic optic neuropathy. Indeed, it is difficult to explain in anatomical terms how hypoperfusion of the posterior ciliary arterial supply could produce such a pattern of visual field loss.

Occasionally, patients report “acute” visual field loss, but in fact have only acutely become aware of long-standing, insidious visual field loss. We doubt this occurred in our patients. Both patients were under regular ophthalmological surveillance, and their visual fields were documented by screening tests prior to their episodes of abrupt visual loss.

In many optic neuropathies, such as those caused by toxins, nutritional deficiencies, or mitochondrial DNA mutations, the small fibers of the papillomacular bundle are selectively destroyed. The converse appears to be true in drusen-associated optic neuropathy: central visual acuity remains normal even when visual field loss is severe (18). This observation is frequently referred to as “Rucker’s rule.” Like most dictums in medicine, it is fallible. Central acuity loss from drusen has been well documented in several reports (9,19,20). These noteworthy exceptions aside, central vision tends to be preserved in patients with optic disc drusen. This finding implies that the small-caliber axons from ganglion cells in the macula enjoy some degree of immunity from the optic neuropathy associated with optic disc drusen. Understanding why these fibers are relatively spared may provide a key to discovering the cause of visual field loss in patients with optic disc drusen. The findings described in this paper indicate that there may be a propensity to spare the papillomacular bundle even when visual field loss is sudden. We caution against the assumption that sudden visual loss in patients with disc drusen represents a manifestation of anterior ischemic optic neuropathy.

REFERENCES

Sudden Visual Field Constriction Associated With Optic Disc Drusen

The article by Moody, Irvine, Cahn, et al. describes two patients who experienced sudden constriction of the visual field of one eye associated with preservation of visual acuity in the setting of impressive drusen of the optic disc. The authors emphasize that it is unlikely that anterior ischemic optic neuropathy was responsible. We have had a similar case. A 75-year-old woman with long-standing disc drusen experienced sudden visual field loss in one eye. The fundus was otherwise normal. There was neither retinal edema, as would be expected with branch artery occlusion, nor disc swelling, as would be expected with anterior ischemic optic neuropathy. We too had no clear-cut explanation for the visual loss. A form of retrobulbar optic neuropathy is possible, but how drusen located in the laminar or prelaminar regions would cause this is unclear. Similarly, there could be some type of effect on ocular perfusion of the retina, causing a generalized hypoperfusion, most marked in the periphery and midperiphery. We did not perform electrophysiologic studies on our patient, but I wonder what an ERG would show. In any event, I agree with the authors that this condition occurs, and I share their confusion regarding the etiology.

Neil R. Miller, M.D.
Baltimore, Maryland
Ocular Ethambutol Toxicity: Is It Reversible?

Atul Kumar, M.D., S. Sandramouli, M.D., Lalit Verma, M.D., H. K. Tewari, M.D., and P. K. Khosla, M.S.

Delayed onset ocular ethambutol toxicity is usually considered to be reversible following prompt withdrawal of the drug. However, in a series of seven consecutive patients with severe visual deficit due to ethambutol toxicity, only 42.2% (3 of the 7 patients) achieved a visual recovery of better than 20/200 after an average follow-up of 8.3 ± 2.1 months after stoppage of the drug. On fluorescein angiography, three cases (42.2%) progressed to optic atrophy during the follow-up with permanent visual damage. There were no predisposing or risk factors to contribute toward the poor visual gain. In this background, we recommend discontinuation of ethambutol from the antituberculous regimen. As an additional side-light, the value of visually evoked potential in the monitoring of patients on ethambutol, especially in cases with early periaxial neuritis, has been emphasised.

Key Words: Ethambutol—Visually evoked potential—Optic neuropathy—Toxicity.

Ethambutol hydrochloride, a bacteriostatic antituberculous drug, was developed in 1962. Since then, mild to severe toxic amblyopia due to ethambutol have been reported by several authors (1-6). The toxic optic neuritis may be early or late onset, may be reversible or irreversible and axial or periaxial (2,5,7-10). Generally, the early-onset toxicity is believed to be irreversible (4,9,11) and due to idiosyncratic reaction (12), though exception exists (7). On the contrary, delayed-onset optic neuropathy is considered reversible (5,8,13,14) and is probably related to the drug’s antimycobacterial mechanism of action as a chelating agent possibly brought about by depleting the eye of zinc (10).

Presently, there are several controversial reports in the medical literature regarding the safety of ethambutol use as a routine antituberculous drug. Our experience with this questionably safe drug was highly discouraging. The present communication highlights the invariably poor visual outcome of the eyes afflicted with ethambutol toxicity.

MATERIALS AND METHODS

Eight consecutive patients who were diagnosed and confirmed to have ethambutol ocular toxicity, on the basis of the clinical features, color vision deficits, visual evoked response (VER), and Goldmann field charting, were included for the study. Ethambutol was stopped immediately after the clinical diagnosis of ethambutol toxicity was made. All the patients were followed up to a minimum period of 6 months with the parameters of clinical examination, including vision recording, color vision, VER, and field charting. All the patients were under treatment with neurovitanins, following the stoppage of the ethambutol. Medical consultation was obtained for ruling out any other systemic problems in all the patients.
RESULTS

The average age of the study group was 39.3 years (range 16-65 years), with equal number of males and females (4 each). All the patients received ethambutol (25 mg/kg body weight) along with isoniazid (300 mg daily), rifampicin (600 mg daily), and B-complex capsules. All the cases except Case 8 presented to us with a sudden diminution of vision of recent onset. The average duration of ethambutol treatment prior to the onset of symptoms was 3.4 ± 2.6 months (range 50 days to 8 months). The average period of follow-up for the first seven cases was 8.3 ± 2.1 months (range 6-12 months). Initially all the patients had an increased latency and decreased amplitude in VER with blue-yellow color vision defects. Central scotoma with or without blind spot enlargement was noticed in the first seven cases. All the first seven cases had a severe reduction in visual acuity as shown in Table 1. At the end of the follow-up, only 3 of the 7 cases (42.2%) had a documented gain in their visual acuity of better than 6/60 (Table 1).

Case 8 presented to us for a routine examination with nonspecific symptoms of itching and had a visual acuity of 6/6 in both her eyes. However, on VER recording, she was observed to have a prolonged latency period with normal amplitude. Her color vision and field charting results were within normal limits. She was followed up for the next month with no further change in her follow-up parameters.

There was no definite correlation of the extent of visual deficit with the period of onset of symptoms following the ethambutol therapy nor with the degree of visual recovery. During the follow-up, on fluorescein angiography, Cases 2, 3, and 7 were documented to have hypoperfusion of the disc, suggestive of optic atrophy in both the eyes.

<table>
<thead>
<tr>
<th>Case no., age, sex</th>
<th>Diagnosis</th>
<th>Time interval between onset of treatment &amp; toxic effects (months)</th>
<th>Follow-up (months)</th>
<th>Best corrected vision</th>
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<td></td>
<td></td>
<td></td>
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CF, Hand movements close to face; FC, Finger counting at one meter.

DISCUSSION

In India, tuberculosis is a highly prevalent disorder, and ethambutol is one of the routinely used drugs as the first line of antituberculous agents along with isoniazid. The usually prescribed dose of ethambutol is 25 mg/kg body weight. The study group was chosen from a multitude of patients who visited our hospital for eye examination with or without symptoms, following ethambutol therapy. The exact statistics are, however, not available.

Delayed-onset optic neuropathy caused by the toxic effect of ethambutol has been known to be dose-related and usually reversible (5,8-10,15). Irreversible ocular toxicity at the dose of 15 mg/kg has also been reported (2). Bouzas and coworkers (3) recorded only one of 14 patients with ethambutol toxicity who suffered from permanently reduced vision. Similar results were published by Orou et al. (16) and Pahlitzsch & Tiburtius (17). In a report by Kakisu et al. (14), 3 of 6 cases had permanently reduced vision, but the drop in vision could be explained in all three cases by risk factors such as diabetes, alcohol abuse, and reduced kidney function. DeVita et al. (18) suggested discontinuation of ethambutol in cases of renal tuberculosis, due to compromise of renal excretion of the drug. Their report highlighted renal dysfunction as a potential risk factor with ethambutol therapy. Smith (19) suggested barring of ethambutol from the antituberculous regime in view of its severe and capricious nature of toxicity. The author's conclusion was based upon his observation of irreversible ocular toxicity despite proper dosage and prompt withdrawal of the drug in four of his patients. Our report of seven cases uniformly presented with severe reduction in visual acuity and showed poor visual recovery in 4 of the 7 cases without any detectable risk factors. Even the visual
recovery observed in the three cases was never 100% in any of the cases. Stoppage of ethambutol and the neurovitamins had no obvious beneficial effects on the recovery of the patients.

Kakisui et al. (14) observed the initial drop in visual acuity following intoxication as the most reliable prognostic factor concerning visual recovery. However, our study revealed a poor correlation with the initial drop in visual acuity. There was overall poor visual recovery in the series, and even in the cases that recovered partially, no reliable parameter could be used as a useful predictor of good visual recovery.

Isoniazid has been documented as a cause of bilateral optic neuritis, especially when used in combination with ethambutol (11). All our cases were continuing to receive isoniazid even when ethambutol was stopped. Isoniazid is presumed to be responsible for the optic neuritis if visual abnormalities persist for 3 months after the discontinuation of ethambutol (11). In this context, whether our cases had irreversible ethambutol toxicity or isoniazid nerve damage remains to be proved.

The mechanism behind the interesting observation of an asymmetrical recovery between the two eyes of Cases 1 and 5 remains unexplained, despite an extensive review of the literature. Similarly, though sporadic incidence of optic atrophy has been reported in the literature, following ethambutol intoxication (20), the documented progress of three cases toward optic atrophy strongly underscores the use of this drug in routine antituberculous regimen.

As mentioned in the literature (9), the central type of optic neuritis following ethambutol therapy was the most commonly observed type of neuritis in our series (7 of 8 cases, 87.5%). Case 8 with good visual acuity and normal color vision, but prolonged latency in VER, perhaps sustained a periaxial optic neuritis. The abnormal VER observed in the case indicates a definite role for monitoring the patients on ethambutol therapy with VER. The case benefited well from cessation of therapy after the detection of the toxicity, although the follow-up was short.

Although ethambutol is claimed to be a potent antituberculous agent (21), despite 30 years of use the safety of the drug is still in dispute (21,22). Incidence of ocular toxicity has been described to be about 5% with dosage of 25 mg/kg, which is the usually prescribed initial dosage for the first 2 months of antituberculous therapy (23). We, however, observed sudden-onset blindness despite proper dosing of ethambutol, careful ophthalmologic follow-up, and prompt discontinuation of ethambutol in initial visual dysfunction. Considering that the role of ethambutol in antituberculous regimen is still arguable (24) and that the drug is a potentially blinding agent as observed in this series, we recommend reconsideration regarding the use of ethambutol as one of the first-line antituberculous drugs. At present, other alternatives are also available and hence the recommendation is extremely feasible.

REFERENCES

Parainfectious Optic Neuritis and Encephalomyelitis
A Report of Two Cases with Thalamic Involvement

Latif M. Hamed, M.D., Jonathan Silbiger, M.D., John Guy, M.D.,
J. Parker Mickle, M.D., Patrick Sibony, M.D.,
Alfred Cossari, M.D., and Mary Andriola, M.D.

Two children developed bilateral severe optic neuritis with thalamic lesions. Both cases were preceded by a viral prodrome, and one case was temporally associated with diphtheria-tetanus-pertussis (DTP) and oral polio vaccination. Both patients favorably responded clinically and radiographically to intravenous corticosteroid therapy, although the first case required long-term immunosuppression.

CASE 1

A 5-year-old girl was referred to Shands Teaching Hospital at the University of Florida for evaluation of a thalamic mass. The patient was in her usual state of good health until 2 weeks prior to admission, when she developed a sore throat, mild fever, and nausea. On the day of admission to another hospital she acutely developed eye pain, gait instability, lethargy, and disorientation. The patient had received her scheduled DTP and oral polio immunizations 3 weeks prior to admission, and had been exposed to a child with viral encephalitis 2 weeks prior to admission. No other significant past medical history was present.

On admission to the outside hospital the patient...
was obtunded but showed no localizing neurological signs. A lumbar puncture revealed a normal opening pressure, WBC = 39, RBC = 5, protein = 29, glucose = 60, and negative latex agglutination, bacterial, and fungal cultures. There was an elevated white blood cell count of 19.5 (74% polymorphonuclear cells) and normal hematocrit, electrolytes, and urinalysis. A magnetic resonance scan demonstrated bilateral thalamic lesions, which showed increased signal on T2-weighted images, but no signs of mass effect (Fig. 1). The patient was treated with ceftriaxone for 2 days with little change in her clinical status. She was transferred to Shands Teaching Hospital for further evaluation.

The patient's clinical examination was essentially unchanged on arrival at our hospital. The patient was begun on intravenous dexamethasone (2 mg every 6 hours). Ceftriaxone (800 mg every 12 hours) was continued. The patient underwent a stereotactic biopsy of the right thalamic lesion. Histopathologic examination revealed chronic perivascular inflammation with microglial activation and microglial nodule formation. Tumor, intranuclear inclusions, and myelin destruction were absent. Stains for herpes viral antigens were negative. Additional studies including erythrocyte sedimentation rate, liver profile, antinuclear antibody, immunoglobulin, complement, C-reactive protein, rheumatoid factor, and meningoencephalitis antibodies (herpes simplex virus, Dengue fever, eastern equine encephalomyelitis, St. Louis encephalitis) showed normal results.

The patient's mental status returned to normal while on corticosteroid therapy, which was tapered as an outpatient. The patient did extremely well for 2 months with normalization of vision. However, 6 days after corticosteroid cessation she developed bilateral eye pain and decreased vision. Visual acuity was 20/400 in the right eye and count fingers in the left eye. There was a left afferent pupillary defect. The left optic nerve head was edematous. Neurological examination was otherwise normal. Magnetic resonance imaging (MRI) of the brain showed encephalomalacia at the site of the biopsy in the right thalamus but was otherwise normal.

After 3 days of intravenous methylprednisolone (10 mg/kg) therapy, visual acuity improved to 20/30 in the right eye and 20/50 in the left eye. The left afferent papillary defect and optic disc edema persisted but were improved. The patient was again discharged on a tapering regimen of oral corticosteroids.

The patient suffered several subsequent recurrences of optic neuritis and altered mental status upon tapering the corticosteroid regimen below 20 mg/day. Imuran was then added to the therapeutic regimen. Six months later, visual acuity was 20/15 in each eye. The afferent pupillary defect and left disc edema had resolved.

**CASE 2**

A 4-year-old girl was examined after admission to University Hospital at State University of New York at Stony Brook for evaluation of papilledema. The patient was in her usual state of good health until 2 months prior to admission when she developed a bifrontal headache, mild fever, vomiting, and diarrhea. This episode resolved spontaneously after 5 days. One week prior to admission the patient complained of headache and ear pain, and was diagnosed with pharyngitis and otitis media. She was treated with oral amoxicillin. Two days prior to admission the mother noted decreased vision, frequent blinking, and clumsiness in the child. The patient had been exposed to chickenpox 9 days prior to admission but never developed a rash.

Visual acuity upon admission was hand motion vision OU. The pupils were sluggishly reactive to light and without a relative afferent defect. There was bilateral disc edema. The general examination revealed erythematous tympanic membranes but was otherwise normal. The patient was awake and alert. Cranial nerves III–XII were intact. She had normal motor and sensory findings and intact reflexes.

A lumbar puncture showed a normal opening pressure, WBC = 16 (83% mononuclear cells), RBC = 8, protein = 26, glucose = 69 (serum glucose = 122). Spinal fluid viral, bacterial, and fungal cultures as well as cytological studies were negative. Other laboratory tests revealed Hct = 35, WBC = 16.4, ESR = 29, C3 = 121, C4 = 28.3, ASO = 200 to 400, RPR negative, rheumatoid factor negative, Lyme titer negative, and negative blood cultures.

MRI with multiple sagittal and axial sections of the brain were obtained using multiplanar spinecho pulse sequences including T1-, proton density, and T2-weighted images. The study revealed an abnormal signal in the left pulvinar of the thalamus measuring over 1 cm with surrounding edema (Fig. 2). There was also increased signal intensity on the T2-weighted images in the gray matter in the posterior parietal regions and left corona radiata (probably representing edema). Re-
FIG. 1. Case 1. (A) T2-weighted MR scan upon initial presentation shows a bilateral thalamic lesion with high signal intensity. (B) T1- and (C) T2-weighted MR scans obtained following treatment with intravenous corticosteroids show total resolution of thalamic lesions; focal encephalomalacia of right thalamus at the site of previous stereotactic biopsy was present. No white matter lesions in the subcortical white matter were seen in this case.

peat MRI 3 days later with gadolinium EDTA and additional views of the orbits showed minimal thickening of the optic nerves and nodular, patchy gadolinium enhancement in the prechiasmal seg-

ments. The thalamic lesion showed minimal enhancement with gadolinium.

The patient was treated with intravenous Solu-medrol 40 mg every day, acyclovir 250 mg/kg/day,
and ampicillin 100 mg/kg/day. During the hospitalization the patient's vision, pupillary reaction, and optic disc edema improved. The patient was discharged after 5 days on a tapering dose of prednisone. She had a recurrent episode of visual loss with papillitis after tapering off the prednisone, but responded well to a slower tapering schedule. One month after the patient's admission her visual acuity was 20/30 OU. The pupils were normal and the disc edema had resolved.

**DISCUSSION**

Optic neuritis is uncommon in childhood and differs from the adult variety in various respects. A study of 41 children with optic neuritis showed a greater tendency for simultaneous bilateral involvement, and a greater frequency of optic nerve edema than in the adult-onset variety (1). Optic neuritis in children is often associated with systemic infections such as measles, mumps, vari-
cella, pertussis, mononucleosis, viral encephalitis, and immunizations (2). Given the high frequency of associated headaches, nausea, vomiting, and spinal fluid lymphocytosis, it may be likely that many cases of childhood optic neuritis are associated with some degree of encephalomyelitis. Even in the absence of these symptoms, some investigators consider many cases of childhood optic neuritis to represent a localized form of encephalomyelitis. Despite the development of optic nerve palsy (88% in one series) the visual prognosis is good in children and the risk of developing multiple sclerosis appears small (4).

Various studies have noted an apparent correlation between childhood vaccinations and the subsequent development of encephalitis and optic neuritis. Optic neuritis has been associated with the following immunizations: DTP, polio, vaccinia (3), measles-mumps-rubella (MMR) (5), influenza (6), rabies (7), and hepatitis B (8). Riikonen (3) studied 18 children with optic neuritis and found 56% had a bacterial or viral infection 2 weeks prior to the first symptom of optic neuritis. Various vaccinations preceded (3 days to 1 month) the first attack of optic neuritis in 5 of 18 patients. Three patients had recurrent attacks of optic neuritis when reexposed to the vaccine. Three patients had meningoccephalitis associated with the optic neuritis. While these studies were not controlled and do not prove causation, they show a temporal relationship between viral infections and/or vaccinations and the development of optic neuritis in children.

In one of our patients, the onset of symptoms was temporally related to a vaccination with DTP and oral polio virus. Common side effects of childhood immunizations including local tenderness, malaise, irritability, and fever are well known and transient. The association of serious and permanent neurological sequelae with certain immunizations remains debatable, however. Miller et al. (9) studied 1,000 children with serious neurological illnesses and found 3.5% were immunized with DTP vaccine 1 week prior to onset of neurological symptoms. They estimated that in an immunized child the relative risk of developing serious neurological illness was 2.4 times that of an unimmunized child. Many authors disagree with the conclusion that serious clinical problems may be caused by the DTP vaccine. A study of 38,171 children who received DTP vaccines during the first 3 years of life showed no increased risk of seizures as compared to a control population (10). Only two patients in the study developed encephalitis, but its onset was greater than 2 weeks after vaccination and neither had permanent sequelae (10). A committee of the Child Neurology Society concluded that no controlled studies have proved the association between pertussis vaccine and progressive or chronic neurologic disorders (11). It should be noted that other vaccines have been more closely associated with serious problems, however. The swine influenza vaccination of 1976 was notorious for a large number of patients developing Guillian-Barre syndrome (6). Smallpox and rabies vaccines were associated with considerable neurological morbidity and mortality (11).

Viral encephalitis can be divided into four distinctive groups: acute viral encephalitis, parainfectious encephalomyelitis, slow viral infections, and chronic viral infections (12). Parainfectious encephalomyelitis (also known as acute disseminated encephalomyelitis) develops 4 to 14 days after infection or immunization. It has similar symptoms and cerebrospinal fluid (CSF) findings to acute viral encephalitis, but no viral particles can be isolated or cultured. The inflammation is probably due to a hypersensitivity reaction as opposed to direct infection, and results in a perivascular mononuclear cellular infiltration and demyelination. Most commonly, parainfectious encephalomyelitis follows nonspecific upper respiratory tract infections (approximately 70%), but may also follow measles, mumps, varicella infections or smallpox and rabies vaccinations (13).

The typical MRI findings in parainfectious encephalitis are multifocal brain lesions, often indistinguishable from multiple sclerosis (14). Our patients presented with thalamic masses in addition to the ophthalmologic findings, and the differential diagnosis included the possibility of a primary thalamic tumor. This was particularly considered in Case 1 due to the solitary nature of the thalamic involvement. This concern led to a biopsy in Case 1. Glial tumors make up the majority of thalamic tumors in children. A retrospective study of 60 children with thalamic tumors revealed 35 to be astrocytomas. Approximately half of these were malignant (15). Even though most germinomas occur in the pineal gland or supracellar region, 5 to 10% originate in the thalamus or basal ganglia (16). It is helpful to obtain a histopathological diagnosis of thalamic tumors, because benign and malignant gliomas and germinomas require different therapeutic approaches (17).

We described the clinical and neuroradiologic findings in two children who developed severe bilateral optic neuritis and thalamic lesions. One patient underwent stereotactic brain biopsy of the thalamus to rule out a neoplasm; the histopatho-
ogy revealed perivascular inflammation. Both patients had an antecedent viral infection and Case 1 was temporally associated with administration of a DTP vaccine. These two cases favorably responded clinically and radiographically to high-dose corticosteroid therapy, and both suffered relapses upon tapering off their corticosteroids. These cases probably represent a clinical variant of parainfectious encephalomyelitis with concurrent papillitis, and point out the need for accurate diagnostic techniques and the need for long-term immunosuppression. Given the striking appearance of the thalamic lesions in Case 1, a decision to treat a similar case conservatively (i.e., with corticosteroids but without obtaining a biopsy) would be a clinical one, and would be difficult to suggest from the neuroimaging alone. However, recognition of this clinical presentation of parainfectious encephalitis may occasionally obviate the performance of a thalamic biopsy.

REFERENCES


Visual Loss as the Initial Presentation of Nasopharyngeal Carcinoma

Ling-Yuh Kao, M.D., Huei-Chun Chuang, M.D., and Yu-Song Liang, M.D.

Eye symptoms and cranial nerve involvement are rather common in nasopharyngeal carcinomas, but early invasion of the optic nerve is very rare. Two cases of nasopharyngeal carcinoma that presented initially with visual loss are reported.

Key Words: Nasopharyngeal carcinoma—Optic nerve—CT scan—Orbital apex compression.

CASE REPORT

Case 1

A 68-year-old male was seen in May 1989 with the chief complaint of progressive right eye visual loss of 3 months duration. Past history revealed that he had suffered from hearing loss in the right ear for 10 years because of chronic otitis media. Eye examination revealed that the vision was no light perception in the right eye, and was corrected to 20/20 in the left eye. The right eye showed an amaurotic pupillary response, but the eye movements and ocular fundi were all normal. Computed tomography (CT) scan demonstrated a space-occupying lesion extending from the right orbital apex to the parasellar area (Fig. 1). A blind biopsy from the nasopharynx was done, and pathologic examination of the specimen revealed "nonkeratinizing squamous cell carcinoma."

The patient received radiotherapy thereafter, but 1 year after completing the radiotherapy, pro-
FIG. 1. CT brain scan of Case 1 showing a space-occupying lesion extended from right orbital apex to parasellar area.

Ptosis and disturbed ocular motility appeared, and orbital invasion by the nasopharyngeal carcinoma became obvious.

Case 2

A 54-year-old male was seen initially in December 1985 at a retina clinic with the chief complaint of progressive right eye blurred vision of one month's duration. Examination revealed a corrected visual acuity of 20/200 in the right eye, and 20/20 in the left eye. The eye movements were normal. Fundus examination disclosed normal optic discs, but some pigmentary mottling was seen at the posterior pole of the right eye. Fluorescein angiography demonstrated some window defects superior to the macula. Under the impression of central serous choroidoretinopathy, a focal retinal photocoagulation was done. However, the visual impairment became worse, and by March 1986 the visual acuity was no light perception in the right eye. The patient did not return until May 1986, when he presented with a blind right eye but with additional signs. Ptosis of the right eye, limitation of eye movement in all directions, and numbness of the right face indicated multiple cranial nerve involvement. A CT scan demonstrated a space-occupying lesion situated at paracavernous sinus and orbital apex area (Fig. 2). Patient was referred to the neurosurgical department and a craniotomy was performed. The tumor mass was removed and the specimen disclosed a "poorly differentiated carcinoma." The orbital and other cranial nerve involvements appeared 5 months after the initial presentation of visual loss, and there were no accompanying nasal symptoms during the whole course of the illness.

DISCUSSION

The common clinical manifestations of nasopharyngeal carcinoma are neck mass, blood-tinged sputum or rhinorrhea, hearing loss, headache, and cranial nerve palsy (2). Cranial nerve involvement was observed in 20-25% of nasopharyngeal carcinoma patients at the first examination (3,4). The 5th cranial nerve was the most commonly affected, followed by the 6th cranial nerve. Isolated optic nerve involvement was rarely reported as the initial manifestation (5,6), but has been frequently found late in the course, and usually associated with extraocular muscle weakness. The optic nerve encasement by tumor was well demonstrated by computerized cranial tomography. Orbital apex in-

FIG. 2. CT brain scan of Case 2 revealed a space-occupying lesion situated at orbital apex and paracavernous sinus area.
Invasion with paracavernous sinus extension without bony destruction was disclosed in these two cases, indicating probably that the lesion went through the foramen lacerum, with the optic nerve invasion (7). The reason why these two cases showed optic nerve involvement first and spared the extraocular muscles at onset remained puzzling.

SUMMARY

Visual loss as the initial presentation of nasopharyngeal carcinoma is very unusual. When a patient experiences progressive visual loss of unknown cause, a detailed nasopharynx and neuroimaging study is indicated, especially in areas of high prevalence.

REFERENCES

Sudden Blindness and Total Ophthalmoplegia in Mucormycosis
A Clinicopathological Correlation

John A. Downie, M.B.B.S., Ian C. Francis, F.R.A.C.S., F.R.A.C.O.,
Jennifer J. Arnold, F.R.A.C.S., F.R.A.C.O.,
Lawrence M. Bott, F.R.C.P.A., and Sue Kos, F.R.A.C.R.

A case of rhino-orbitocerebral mucormycosis is presented, illustrating the serious nature of this disease. Clinical features and their pathological correlations are demonstrated. The need for a high index of clinical suspicion, and an early biopsy of the affected area is emphasized so that the benefits of early diagnosis and therapy may be gained.

Key Words: Mucormycosis—Rhino-orbitocerebral.

CASE HISTORY

An 86-year-old man was admitted to our hospital with a 1-week history of lethargy, anorexia, and thirst. The patient had diffuse interstitial pulmonary fibrosis and secondary right ventricular cardiac failure, as well as atrial fibrillation and mild chronic renal failure. Oral corticosteroids had been commenced 3 weeks prior to admission to treat the patient's respiratory disease.

On examination at the time of admission, he was lethargic, dehydrated and in atrial flutter. Fine basal crepitations were present in both lung fields. No neurological deficit was present.

A full blood count showed a white cell count of $14.2 \times 10^9/L$ (89% neutrophils, 8% lymphocytes, and 3% monocytes), a haemoglobin of 16.3 g/dl and a platelet count of $114 \times 10^9/L$. Serum biochemistry showed: sodium 121 mmol/L, potassium 4.4 mmol/L, urea 20.9 mmol/L, and creatinine 0.20 mmol/L. The blood sugar was 11.5 mmol/L, and there was glycosuria but no ketonuria.

Free fluids were allowed, diuretics ceased, and digoxin commenced. The patient improved clinically over the next few days, but subsequently complained of painful, stinging eyes on day 3 post-admission, and of a bifrontal headache on day 4 postadmission. On the morning of day 5 he was found to be drowsy, confused, thirsty, and polyuric. Over the next few hours a low fever (37.7°C) and neurological signs developed.

Right-sided ptosis and total internal and external ophthalmoplegia were present. The right eye demonstrated no perception of light, and the right corneal reflex absent. The right fundus was normal, as was the left eye and the remainder of the neuro-ophthalmological examination.
Microscopic Findings

Sections through the posterior orbit showed widespread necrosis involving nerves, arteries, and muscles. Fungal hyphae consistent with mucormycosis were seen on haematoxylin and eosin, and on methenamine silver stains in the area of necrosis (Fig. 4).

Fungal hyphae were seen infiltrating the walls of some arteries and veins traversing the necrotic area, with consequent thrombosis of these vessels (Fig. 5). An associated neutrophilic inflammatory reaction was present (Fig. 6). Sections of the ophthalmic artery at 15 mm from the optic foramen showed involvement in this process, although thrombosis was not seen. However, some vessels that traversed the area of necrosis were uninvolved (Fig. 7).

In the posterior orbit, sections of the optic nerve showed it to be infarcted, infiltrated by fungal hyphae, and to have an associated neutrophilic inflammatory reaction. Proximal to the optic foramen, the nerve showed infiltration by fungal hyphae with associated necrosis. The optic chiasm showed foci of necrosis, but no fungal hyphae were seen.

Although cultures of the necrotic material were negative, the postmortem findings confirmed rhino-orbitocerebral mucormycosis, with involvement of the right-sided maxillary, ethmoidal, and sphenoidal sinuses and the posterior orbital contents. Infiltration of the organism through vessel walls, particularly the ophthalmic artery,
MUCORMYCOSIS

DISCUSSION

Our patient illustrates the orbital apex syndrome in rhino-orbitocerebral mucormycosis. Mucormycosis is a rare, severe infection caused by fungi of the class Phycomycetes (1). These are ubiquitous, and inhabit the respiratory tract (2-7). Only the subclass Zygomycetes contains pathogenic fungi, which almost all belong to the order Mucorales. The most common are the genera Absidia, Mucor, and Rhizopus (1,3,4,6,8-10). They are normally saprophytic and nonpathogenic.

Six clinical syndromes in mucormycosis are defined: rhino-orbitocerebral, pulmonary, gastrointestinal, cutaneous, disseminated, and miscellaneous (4).

Rhino-orbitocerebral mucormycosis is the most common and distinctive of these syndromes. It encompasses nasal, orbital, and cerebral infections (8-11). In 50% of cases there is orbital involvement (12). There is also a particular association of this

The right optic nerve, swollen in its intracranial course. The left optic nerve is normal.

FIG. 2. A necrotic focus in the right posterior orbit.

FIG. 3. A necrotic focus in the right posterior orbit.
syndrome with diabetes—80% in Schwartz's series (1).

Infection usually occurs in debilitated patients and only rarely in normal individuals (1-12, 14). In the setting of normal cellular or humoral immunological defences, the airborne spores are contained by the body's phagocytic response (1, 2, 15).

Diabetes mellitus is the most common underlying condition, particularly when it is associated with acidosis (1-8, 10-12, 14, 16). In diabetic ketoac-
MUCORMYCOSIS

FIG. 6. Histopathology of a small artery traversing a necrotic area, demonstrating invasion of its wall by mucor hyphae, vessel thrombosis and an associated neutrophil reaction (Hematoxylin and eosin; ×180.)

Idiopathic there is impairment of phagocytic function and mast cell degranulation, which, in addition to the acidic and glucose-rich environment, favours growth of the fungi (1,6,10,11).

There are many other conditions associated with mucormycosis, the lymphomas and leukemias being the most prominent (3,6,8,9,11,14). Our patient was typical of the group at high risk.

FIG. 7. Histopathology showing a viable medium-sized artery traversing an area of necrosis. (Hematoxylin and eosin; ×720.)
of developing mucormycosis in a diabetic (although not acidic) secondary to the recent introduction of corticosteroids. He was further debilitated by severe underlying diffuse interstitial pulmonary fibrosis, chronic renal failure, and his dehydrated state at the time of admission.

The degree to which corticosteroid use is a risk factor in the development of mucormycosis is debated. Parfrey has presented 3 patients, in a series of 33 with mucormycosis, whose infection was related to corticosteroid—induced hyperglycaemia (8). By itself, corticosteroid use probably does not represent a predisposing factor for the development of mucormycosis, but does enhance the spread of the established disease (1).

The spread of mucor organisms to adjacent tissues is rapid, and may be direct, through contiguous structures, or via vessels or neural tissue (1,3).

Following inhalation of the spores, the primary infection is a naso-oropharyngitis (1,4,7,11,14,15). From the nose, or palate, infection typically spreads to the adjacent paranasal sinuses, and from these may reach the orbit. From the posterior orbit, and sometimes from the nose via the cribiform plate, mucormycosis may reach the brain (1,4,7,8,10,11,15).

Rhino-orbitocerebral mucormycosis has a number of clinical presentations including sinusitis, orbital cellulitis, the orbital apex syndrome, hemiparesis, depressed consciousness, or nasopharyngeal mucormycotic osteitis (4).

The disease process is typically unilateral, as in our patient (1,2,7). The most common initial symptoms and signs are sinusitis, nasal discharge, orbital pain, and facial cellulitis. Lethargy and visual loss may also be early features (3).

Nasal involvement results in an early low fever, purulent sanguineous nasal discharge, and a black eschar seen on the nasal turbinates, septum or palate. These features, along with obtundation, were cardinal signs of mucormycosis in our patient.

The development of a black nasal eschar occurs in 47% of cases but is not a reliable early sign of the disease (1,3). An altered mental state, present in 61% of cases of rhino-orbitocerebral mucormycosis, is a more common sign (1).

Orbital invasion by mucormycosis is marked by pain, cellulitis, chemosis, and proptosis. Periorbital swelling or necrosis can develop (1,3,6,9). Visual loss, the orbital apex syndrome, and direct involvement of the globe may occur (1,4,6,7,10,11,14,15).

The orbital apex syndrome comprises visual loss, complete internal and external ophthalmoplegia, and dysfunction of the ophthalmoplegic division of the trigeminal nerve (4,17). It occurs early in our patient's acute illness, and is a characteristic presentation of rhino-orbitocerebral mucormycosis. In Schwartz's series, fifth cranial nerve palsy was noted in 66% of cases, third cranial nerve palsy in 64% of cases, and fourth cranial nerve palsy in 63%. Internal ophthalmoplegia occurred in 56% of cases, corneal anaesthesia in 26%, and visual loss in 46% (1).

The differential diagnosis of the orbital apex syndrome is wide (17). It includes orbital lesions such as haemorrhage, cellulitis, pseudotumour, and the vasculitides; cavernous sinus lesions including septic thrombosis, aneurysms, and caroticocavernous fistulae, and tumours, including those of the orbit, sinuses, and nasopharynx (17).

Differentiation between the orbital apex syndrome and septic cavernous sinus thrombosis (in which there is total ophthalmoplegia and trigeminal nerve involvement without blindness) may be difficult. Visual loss and proptosis are, however, rare in cavernous sinus thrombosis (6,7).

Cerebral involvement may be direct, with abscess formation, or be due to fungal invasion of cerebral vessels producing cerebral infarction. Obtundation, convulsions, and hemiplegia may ensue. Cavernous sinus thrombosis and thrombosis of the internal carotid artery are common (1,3,4,7,10,11,14,15).

The pathological findings in our case were characteristic of the disease. The organism has a propensity for invading vessel walls, producing thrombosis and subsequent ischaemic necrosis of surrounding tissues (1,3,4,7,11,12). The resultant necrotic tissue is a characteristic grey-black, and accounts for the "black eschar," which is a feature of the disease (3,11).

Selective vessel and tissue invasion by fungal hyphae was present in our patient at autopsy, along with tissue necrosis involving the posterior orbit and adjacent paranasal sinuses. The sparing of some ciliary and the retinal vessels was seen histologically, and this probably accounted for the continued viability of the anterior orbital structures, including the anterior segment of the eye, the choroid and the retina. It is most likely that this feature of vascular sparing simply represents an early stage in the evolution of rhino-orbitocerebral mucormycosis in our patient.

The reaction of the body to tissue invasion by mucor organisms is generally an intense neutrophil infiltrate about the infarcted tissue. This was observed in our patient. In 33% of cases a neutrophil infiltrate about the fungal hyphae themselves.
MUCORMYCOSIS

has been reported (1). Rarely, a granulomatous inflammatory response is seen.

Bony necrosis of the walls of the paranasal sinuses was prominent in this case. This was due to the extensive infarction as a result of vessel thrombosis, and this provided a means of spread of the infection between contiguous tissues.

Visual loss in this case may have been due to infarction of the intracranial part of the optic nerve or to direct fungal invasion of the intracranial part of the nerve and the optic chiasm. Optic nerve infarction is well described, while invasion of the nerve by mucor organism is noted by only a few authors (1,15). Optic nerve involvement is also a mechanism by which the organism may reach the brain.

Cranial nerve palsies in mucormycosis may be the result of infarction of the nerve, or of direct fungal invasion, as occurred in our patient (3).

Ophthalmic artery wall invasion and necrosis was prominent in this case, but had not resulted in thrombosis of the artery. Ophthalmic artery thrombosis is, in fact, a rare autopsy finding (1). Invasion of this artery’s wall is illustrative of the organism’s predilection for vessels, and of a further mechanism by which it may reach the brain (1,7,14,15).

The principles of management of rhino-orbitocerebral mucormycosis are early diagnosis, systemic antifungal therapy, surgical debridement of devitalised tissues, and control of the underlying disease processes (1–8,11,12,15). Early diagnosis has improved markedly in the past two decades, and contributed significantly to the reduced mortality of the disease since the 1950s (8).

Diagnosis follows from clinical suspicion and histological confirmation in biopsy specimens, as in our case (1,8). Culture of the biopsy specimen is often negative, probably because preparation of the tissue for culture (usually grinding) destroys the hyphal cell wall and the viability of the fungi (Personal communication, 1988: D. Muir, Senior Mycologist, Australian National Reference Laboratory in Medical Mycology, Royal North Shore Hospital, Sydney, Australia). As well, specimen collection at autopsy (after storage of the body at 4°C) and antifungal therapy may lead to a low inoculum for culture.

Histological stains demonstrate tissue invasion by broad (6–50 μm), nonseptate hyphae with right-angle branching (1,2,6,8,10,13–15). The organism is seen with hematoxylin and eosin staining, but is best demonstrated by methenamine silver or periodic acid-Schiff stains.

Except where magnetic resonance imaging (MRI) is available, computed tomography (CT) scanning is the radiological method of choice in the evaluation of these patients, and it can be used to guide surgical debridement (16). Findings include paranasal sinus involvement with mucosal thickening and fluid levels, as in our case.

Bony destruction is infrequently seen on a CT scan (3,5,16) and was absent in our case despite the intense bony necrosis seen later at autopsy. Features of orbital involvement include preseptal oedema, proptosis, increased density of the involved fat of the orbital apex, thickening of the medial rectus muscle, optic nerve enlargement, and nonenhancement of the superior ophthalmic vein or ophthalmic artery (3,5,7,16,18). Nonenhancement of the superior ophthalmic vein has been considered to be specific for orbital apex mucormycosis (16,18). In our case, the superior ophthalmic vein was of increased density, enlarged, and did enhance. We feel that this represents the effect of orbital apex congestion in this disease, and is simply a stage before thrombosis of the vein and thus loss of contrast enhancement.

Aggressive surgical debridement of the necrotic tissue, in conjunction with systemic amphotericin B therapy, gives the best survival (10). Mortality is now reported to be between 15 and 35%, and is lower in those patients in whom the predisposing condition is diabetes (6,11). In 70% of survivors there may be severe residual defects or disfigurement (6).

REFERENCES


Transient Cortical Blindness Due to Hypertensive Encephalopathy
Magnetic Resonance Imaging Correlation

Thomas R. Marra, M.D., Meenaxi Shah, M.D., and Mary Ann Mikus, D.O.

Striking reversible signal intense magnetic resonance imaging (MRI) lesions were observed in the occipital cortex of a 16-year-old girl who presented with an attack of transient cortical blindness as the initial manifestation of hypertensive encephalopathy (HTE). The lesions were seen to best advantage on T2-weighted imaging and were not visible on computed tomography (CT). It is proposed that such occipital lobe MRI lesions likely reflect extravasation of fluid and proteins across the blood brain barrier, damaged as a consequence of cerebral autoregulation failure.

**Key Words:** Hypertensive encephalopathy—Magnetic resonance imaging—Cortical blindness.

REPORT OF A CASE

A 16-year-old Native American girl with a history of chronic renal failure due to biopsy-proven mesangial proliferative glomerulonephritis developed an episode of sudden total loss of vision lasting for several minutes while walking between classes in a school corridor. This was followed by a generalized tonic-clonic seizure. Upon presentation in the emergency department, the patient was noted to be confused, agitated, and combative, but without focal visual, motor, or sensory abnormalities noted. Blood pressure ranged from 224/122 to 230/152. Her pulse was 120 and regular. Respirations were 20 per minute. She received a bolus of intravenous diazepam and phenytoin 15 mg/kg was administered. A nitroprusside drip was started and she was admitted to a monitored bed. A comprehensive bedside neurologic examination was performed the following day. At this time, the
patient was alert, oriented, cooperative, and without visual complaint. Blood pressure was 160/110. There was normal cranial contour and the neck was supple without evidence of nuchal rigidity. The pupils were equal in size and measured 6-7 mm in diameter. They reacted briskly to light and accommodation. No afferent pupillary defect was noted. Visual acuity as measured by Snellen card was 20/25-2 (OD) and 20/20 (OS). Visual fields were full to confrontation testing employing red and green test stimuli. The funduscopic examination revealed 1+ diopter of papilledema in the right eye and an indistinct temporal disc margin in the left eye. Arteriolar narrowing but no retinal hemorrhage or exudate was noted. Ocular motility and saccadic eye movements were normal. The remaining cranial nerves were normal. The deep tendon reflexes were symmetrically brisk (3+3+1) with some reduplication in both upper and lower extremities, but there was no Babinski sign. There was no focal motor, sensory, or cerebellar deficit. Gait, station, and Romberg testing were normal.

Laboratory results were remarkable for a hemoglobin of 10.7 g/dl; hematocrit, 31%; sodium, 143 mmol/L; potassium, 3.5 mmol/L; chloride, 103 mmol/L; bicarbonate, 27 mmol/L; BUN, 86 mg/dl; and creatinine, 7.7 mg/dl. The serum renin level was elevated at 28.6 ng/ml/h. The urinalysis revealed microscopic hematuria and proteinuria (>300 mg/dl). Because the authenticity of the patient's seizure was initially questioned by emergency room personnel, a serum prolactin level was obtained within 1 hour of the episode and this was significantly elevated, 79.6 ng/ml. An MRI scan performed the day of admission in the non-acquisition mode on a GE 9800 scanner was normal. An electroencephalogram was obtained the following day and revealed no definite focal, diffuse, or paroxysmal disturbance of cerebral function. A renal ultrasound demonstrated diffuse increase in the echogenicity of the kidneys consistent with depressed renal function. An MRI scan was obtained on the second hospital day at a time when the patient's mental status had cleared and she had no visual complaints. Spin density and T2-weighted axial images demonstrated multiple focal areas of increased cortical signal intensity with disproportionate involvement of the occipital lobes (Fig. 1).

The patient's blood pressure was brought under control with an oral calcium channel blocking agent and an angiotensin-converting enzyme inhibitor. An interval MRI scan performed 9 months later showed complete resolution of the previously noted areas of increased cortical signal intensity (Fig. 2).

DISCUSSION

Our patient satisfies the accepted clinical criteria for the diagnosis of hypertensive encephalopathy (4) and this was likely of renal vascular origin. HTE is a medical emergency characterized by abrupt severe elevation of blood pressure. The symptoms of HTE include headache, nausea, vomiting, visual disturbance, confusion, and focal or generalized weakness. Signs include disorientation, obtundation, focal neurologic deficits, generalized or focal

![FIG. 1. T2-weighted (SE 2000/80) magnetic resonance images obtained 24 hours after admission demonstrate multiple areas of increased signal intensity with disproportionate involvement of the occipital cortex. A noncontrast computed tomographic scan obtained at the time of admission had been normal (not pictured).](image-url)
seizures, retinopathy, and papilledema. The syndrome is reversible, usually within a few hours of blood pressure reduction. HTE is considered a diagnosis of exclusion and care must be exercised to exclude stroke, subarachnoid hemorrhage, intracranial mass lesions, seizure disorder, cerebral vasculitis, and encephalitis. HTE is thought to be due to a failure of cerebral autoregulation triggered by a sudden rise in systemic blood pressure causing fibrinoid necrosis of arterioles and capillaries leading to extravasation of fluid and protein across the blood-brain barrier into the surrounding brain parenchyma (3,4). The CT scan may show reversible white matter hypodensity as an indication of this process (5). Hauser and colleagues (6) recently reported reversible MRI abnormalities characterized by focal, symmetric increased signal intensity involving both gray and white matter in three cases. They postulated that the high-intensity lesions seen on MRI reflect this process of fluid and protein extravasation. Similarly, resolution of the lesions would reflect their reabsorption.

The MRI of our patient whose hypertensive crisis was ushered in by an attack of cortical blindness revealed striking focal high signal intensity lesions in the occipital lobes. These changes were seen to best advantage on T2-weighted (SE 2,000/80) imaging and were not associated with any significant mass effect or cortical effacement. At the time the MRI was obtained, the patient was neurologically normal and free of visual complaints, leading us to conclude that persistence of vasogenic edema rather than cerebral infarction was the likely pathologic substrate. An interval MRI scan obtained 9 months later, indeed, showed complete resolution of the high signal intensity lesions and no sign of occipital lobe infarction.

Since our patient, and the three patients presented by Hauser and coworkers all showed similar MRI T2 signal intense lesions disproportionately involving the occipital regions, and each of these patients had prominent, but evanescent, visual manifestations, it is suggested that these MRI lesions may represent the pathologic substrate of the transient cortical blindness of HTE. These changes are likely due to extravasation of fluid and protein across the blood-brain barrier. Why vasogenic edema per se would cause transient cortical blindness is unclear. We speculate that it may not be the cause but rather is an epiphenomenon of occipital lobe ischemia, the result of intense cerebral vasospasm triggered by malignant systemic hypertension.

REFERENCES

Tonic Pupil in Lymphomatoid Granulomatosis

Sajjad Haider, F.C.Ophth.

Tonic pupil is due to a lesion of orbital parasympathetic neurons in the ciliary ganglion or short ciliary nerves (1). Precise etiology of the condition remains obscure. In the case described here, development of "tonic pupil" was followed by systemic features typical of lymphomatoid granulomatosis, and diagnosis was confirmed by histology of the skin rash. This case underlines the heterogeneity of the causes of tonic pupil. Vascular occlusion can be a possible mechanism in the pathogenesis of tonic pupil.

**Key Words:** Tonic pupil—Lymphomatoid granulomatosis.

Lymphomatoid granulomatosis is a postthymic angiocentric T-cell proliferation (2) causing obstruction of arterial lumina. Commonly involved organs are lungs, skin, and central and peripheral nervous system. There are no ocular features characteristic of the condition. Uveitis and eyelid involvement (3), bilateral peripheral retinal vasculitis with posterior uveitis (4), and, more recently, choroidal involvement (5) have been reported. Tonic pupil has never been described in this illness.

**CASE REPORT**

A 31-year-old Caucasian male was seen in the ophthalmic department while convalescing from a laparotomy (3 days earlier). He gave a history of blurring of vision in the left eye for 2 weeks. His visual acuity was 20/15 in the right eye and 20/30 in the left, improving to 20/20 with a pinhole. The left pupil was dilated to 6 mm, only sluggishly reactive to light and near stimulus. On slit lamp microscopy the reaction to light was found to be sectoral and tonic. On instillation of pilocarpine 1%, the left pupil constricted to 3 mm. The knee reflexes were intact. An orbital computed tomography (CT) scan was reported as normal. A photograph of the patient taken 6 months previously, enlarged to study the size of the pupils, showed the pupils to be equal. This proved the pupil abnormality to be recent. The patient was examined 4 weeks later. All the parameters were the same except the pupil reflex to near, which had improved. This development of light near dissociation at the second consultation, confirmed the diagnosis of tonic pupil and proves it to be as recent as 1 month.

He had been admitted on the surgical floor the previous week with sudden-onset umbilical pain accompanied by nausea. He later vomited and pain became generalized. An exploratory laparotomy showed ischaemic small bowel and enlarged mesenteric lymph nodes, which were resected. Histology of resected specimen showed ischaemia...
and mesenteric arterial thrombosis with low-grade vasculitis affecting medium-sized vessels. He later developed a fluctuating pyrexia with exacerbations at night and night sweats, glove stocking paresthesia, and an itchy rash (erythematous indurated plaques) on his extremities. Viral titres, antibody screen, and blood cultures were all negative. The ESR was normal at 15. The only positive laboratory findings were transient opacification on chest x-ray, a raised value of C-reactive protein (16 mg/L), and neutropenia (white cell count, 2.5), but a bone marrow showed no abnormality. A skin biopsy of the rash showed an angiocentric T-cell lymphoma. The morphology and infiltrative pattern was suggestive of lymphomatoid granulomatosis.

**DISCUSSION**

The precise etiology of tonic pupil remains unknown, but viral infections have been suspected to be responsible. Sera from 75 consecutive patients with Adie's tonic pupil, examined for viral and microbial antibodies, however, showed no significant elevation (6). In a recent report, human parvovirus B19 was linked with Adie's pupil in an 18-year-old woman (7). Chickenpox (8) has also been implicated. It is possible that tonic pupil in the latter was due to orbital vasculitis, which is a recognised complication of varicella-zoster infection (9). Another case of tonic pupil was reported in a patient with temporal arteritis (10). In the case described above, development of tonic pupil was followed by systemic features typical of lymphomatoid granulomatosis. This temporal sequence points to lymphomatoid granulomatosis as the cause. It is suggested that vascular occlusion can be a possible pathogenic mechanism for the development of tonic pupil.

**REFERENCES**

The Four-Meter Confrontation Visual Field Test

Sylvia R. Kodsi, M.D. and Brian R. Younge, M.D.

Confrontation visual fields have limited value in testing paracentral vision. We have used a four-meter confrontation test for several years at the Mayo Clinic for screening of the central field. This test can identify paracentral scotomas and macular sparing in a homonymous hemianopia. The optics of this technique parallel those of the two-meter tangent screen examination in which a scotoma is greatly enlarged by doubling the test distance. Although in common usage by some neuro-ophthalmologists, this simple technique is useful as an office screening device for evaluating paracentral vision.

Key Words: Kinetic technique—Static technique—Macular function.

Ophthalmologists and neurologists have seen visual field tests evolve from various confrontation visual field tests to computerized automated perimetry. However, it remains a challenge to identify visual field defects by confrontation tests prior to performing formal visual field tests or when formal visual field tests are unavailable. In this article we describe a confrontation visual field test that was originated by Dr. Thomas P. Kearns and has been used at the Mayo Clinic for more than 30 years. We call this the four-meter (4-m) confrontation visual field test. This test is extremely valuable as a supplement to the standard confrontation visual field test done at 0.5 m, especially in detecting small paracentral scotomas. It is easy to perform, takes but a few seconds, and costs nothing, and as far as we know, this test has not been described in the literature.

An examiner can perform confrontation visual field tests by kinetic or static techniques (1). With kinetic techniques, the examiner’s fingers or an object is moved from the periphery toward fixation and the points where the patient first becomes aware of the target are identified. Confrontation visual field testing by the static method is usually by the finger counting method, which was first described by Welsh in 1961 (2). The examiner presents one or two fingers in each of the four quadrants of the visual field and the patient identifies the number of fingers seen.

Static visual field testing is much more sensitive than kinetic visual field testing for quantitative perimetry. In both the kinetic and the static methods of confrontation visual field testing, previous literature described testing distances of 1 m or less, with the average distance close to 0.5 m (1-5). Although confrontation visual field testing at 0.5 m is excellent for detection of large visual field defects, small paracentral or arcuate defects that can occur with occipital lobe infarcts, ischemic optic neuritis, glaucoma, and early chiasmal lesions may escape detection. Often the presenting complaint of these
FOUR-METER VISUAL FIELD TEST

patients is difficulty in reading secondary to missing parts of letters or words. If the examiner uses the 4-m confrontation visual field test in addition to the standard 0.5-m test, there is a better opportunity to identify these defects.

The 4-m confrontation visual field test originates from the same concept that is used to identify the hysterical patient or malingering with a markedly constricted visual field. In this situation, a tangent visual field test is performed at testing distances of 1 m and 2 m. If an organic basis exists for the constricted visual field, then the size of the visual field will enlarge appropriately when the results of the 1-m test and the 2-m test are compared. However, if there is hysterical field loss or feigned field loss, then the visual field will remain the same size at 1 m and 2 m (Fig. 1). This has also been described in the past as funnel and tunnel visual fields, respectively (3). Thus, the size of a normal patient's visual field will enlarge as one increases the distance from the patient to the tangent screen if the target size remains relatively constant.

It is generally wise always to perform the standard 0.5-m confrontation visual field test prior to the 4-m test. This educates the patient in correctly fixating straight ahead and ensures more accurate fixation at the longer distance. The examiner backs away 4 m from the patient to perform the 4-m test. While the patient occludes one eye, the examiner presents one or two fingers in various quadrants. The patient identifies the number of fingers present while maintaining fixation on the tip of the examiner's nose. Also, simultaneous presentation of one or two fingers in the opposing nasal and temporal fields can be used to detect the extinction phenomenon or for comparison of hemifields. In the presence of a homonymous defect, the examiner can also perform the 4-m test by moving the finger from the periphery toward the fixation point and identifying the point where the patient first sees the target, thus obtaining an estimate of macular sparing or its absence. Both eyes can be opened if a homonymous scotoma exists, assuming the patient fixates binocularly.

The area of a scotoma increases by a factor of 64 when the testing distance increases from 0.5 m to 4 m (Fig. 2). This increase in the area of the small paracentral scotoma explains why the 4-m confrontation visual field test can easily identify small paracentral visual field defects that the 0.5-m confrontation visual field test is unable to locate.

The increase in area of the visual field at 4 m allows us to identify small paracentral scotomas; however, this increase in area limits the 4-m confrontation visual field test to detection of central or paracentral defects. To further explain the limitations of this test we can return to the example of the optic nerve scotoma.

If the examiner's nose is the fixation target, then the average examiner's arms are too short to locate the blind spot with the 4-m confrontation visual field test (Fig. 3). Therefore, the 4-m confrontation visual field test can only detect scotomas that are closer to fixation than the blind spot.

The following examples illustrate the value of the 4-m confrontation visual field test. A patient may have a small central homonymous hemianopia if a tiny infarct involving the occipital lobe has occurred. This defect may only involve the central 5° to 10° near fixation and may escape detection by standard confrontation test. However, when the examiner moves away from the patient to a distance of 4 m, the scotoma will enlarge enough so that the examiner can easily detect the small central homonymous hemianopia.

![Diagram of optic nerve and blind spot](image)

**FIG. 2.** The optic nerve is projected in space as a blind spot with dimensions w x x at 500 mm, and these increase to y x z at 4,000 mm.

The visual field in Fig. 4 is from a patient with a central left homonymous hemianopia that we were unable to detect by the standard 0.5-m confrontation visual field test. However, it was easily identified by the 4-m test. The patient's visual field also demonstrates the concept of enlargement of the scotoma by increasing the testing distance while maintaining the size of the target relatively constant. Other examples of difficult visual field defects to detect with the standard confrontation visual field test at 0.5 m would be the small altitudinal paracentral defect often seen in ischemic optic neuritis or low-tension glaucoma. Again, these scotomas may be too small to detect by confrontation visual field testing at 0.5 m; however, at 4 m the examiner can locate the scotoma.

Although the major purpose of the 4-m confrontation visual field test is to detect small paracentral scotomas, it is also of value in the detection of macular sparing in hemianopic and quadrantanopic defects. The standard confrontation visual field technique will detect the presence of a homonymous hemianopia or a quadrantanopia but the examiner may not be able to identify them if macular sparing is present. However, the 4-m confrontation visual field test will indicate macular sparing if the patient can identify the fingers present in the hemianopic or quadrantanopic field at 4 m.

The following case illustrates the examiner's ability to detect macular sparing with the 4-m confrontation visual field test. A 31-year-old woman was cortically blind secondary to anoxic encephalopathy. Her visual acuity was 20/25 in both eyes; however, she did not have any peripheral vision. We were unable to detect the extent of her macular sparing with the standard 0.5-m confrontation visual field test. However, with the 4-m confrontation visual field test we found that she had a complete right homonymous hemianopia and a left homonymous hemianopia with macular sparing, demonstrated later with tangent visual field testing (Fig. 5).

Another application of the 4-m confrontation visual field test is in detecting functional vision loss (hysteria or malingering). If a patient is shown to have a markedly constricted visual field of organic

FIG. 3. At 4 m, the distance of the blind spot from the point of fixation, in this case the examiner's nose, is outside the reach of the examiner's arm. The area of field being tested is within 5° to 10° of fixation.

FIG. 4. Homonymous scotoma that enlarged to about twice the size at 2 m in a patient with an occipital stroke. This was not found by the usual confrontation test up close, but it was easily detected at 4 m. Note that it comes right up to fixation.
FOUR-METER VISUAL FIELD TEST

etiology by standard 0.5-m confrontation visual field testing, then the visual field test should not be constricted at 4 m because only the control 10° is being tested. However, a malingerer or a hysterical patient with a constricted visual field will exhibit “tunnel vision” and will also have a constricted field at 4 m. The visual field in Fig. 6 demonstrates tunnel fields in a young woman with functional vision loss who demonstrated a markedly constricted visual field at 0.5 m and at 4 m.

Additional applications of the 4-m confrontation visual field test include testing the visual field of very young children, elderly demented patients, and patients in intensive care units. All of these individuals may not be able to perform formal visual field tests, and the 4-m test is an extremely useful supplement to the standard 0.5-m test in the evaluation of these patients. Lastly, the 4-m visual field test can be done by color comparison along the vertical or horizontal meridian to detect subtle paracentral scotomas that may occur secondary to an optic neuropathy or glaucoma.

In summary, the 4-m confrontation visual field test has been successfully used at the Mayo Clinic for many years in addition to the standard 0.5-m confrontation visual field test. The 4-m confrontation visual field test is a test of macular function and can identify small central or paracentral scotomas that the examiner may not find when the patient is only tested at 0.5 m. It is not meant to supplant or substitute for more formal perimetry but often provides additional clinical information of importance in explaining symptoms. It takes but a few seconds to perform in patients whose history suggests paracentral defects. Also, one may identify macular sparing in homonymous hemianopias and quadrantanopias with the 4-m confrontation visual field test. We recommend the addition of this simple clinical test on appropriately selected patients in addition to the standard 0.5-m confrontation visual field test to obtain the most information possible by confrontation visual field tests.

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Linear Nevus Sebaceous Syndrome

Alan M. Roth, M.D. and John L. Keltner, M.D.

The pathologic terms hamartoma, choristoma, nevus, and phakoma often are confused. We discuss them in relation to a patient with the linear nevus sebaceous syndrome who had a large limbal mass that grew unusually rapidly and was excised. Histopathologic examination showed that it was a complex choristoma composed of lacrimal gland, adipose tissue, and myxomatous tissue. The latter has not been described previously in this disorder. This neuro-oculocutaneous syndrome has been considered one of the phakomatoses.

Key Words: Nevus sebaceus—Conjunctiva—Complex choristoma—Myxoma—Lacrimal gland—Adipose tissue—Phakomatosis.

CASE REPORT

The patient is a 17-year-old mentally retarded boy we first saw at the Department of Ophthalmology of the University of California, Davis in September 1986 with the diagnosis of linear nevus sebaceous syndrome. He had dysmorphic facies and a history of seizures (both grand mal and Jacksonian), mild right hemiparesis, and hydrocephalus, which had required placement and revision of a ventriculoperitoneal shunt. Computed tomography (CT) of his head showed left hemisphere atrophy and hypertrophy of cranial and mandibular bones. He also had multiple recurrent hemangiomas of the face and mandible, one of which caused massive hemorrhage requiring transfusion during surgical resection in 1979. His foster mother stated that he had a red vascular-appearing growth on his left eye, which was first seen when he was age 5, and which had slowly grown and encroached on the cornea. There had been multiple episodes of enlargement and recession, but, over the prior several months, it had steadily enlarged.

Examination on September 26, 1986 showed visual acuity of 20/400 in the right eye and questionable light perception in the left. There was a 2.5-cm soft red mass at the left nasal corneoscleral limbus. Extraocular movements were restricted in both eyes, and the ocular fundus was normal on the
right, but couldn't be seen on the left. We ordered a CT scan of his left orbit, but this could not be performed without sedation, which the mother refused. The boy was scheduled to have the mass excised as a presumed hemangioma, but this was canceled on October 7 after the history of the previous intraoperative hemorrhage was revealed, and we elected to observe him.

By November 6, the lesion had grown considerably and appeared to be very friable (Fig. 1). Because of the rapid growth, we feared that it was neoplastic and might bleed spontaneously. We decided to remove it with the CO₂ laser, and did so without incident on November 19 (without need for the two units of blood on hold). A tarsorrhaphy was performed. There has been no evidence of recurrence of the lesion to date.

PATHOLOGY FINDINGS

Specimen was a hemispheroid of epithelial-covered soft tissue measuring 27 x 25 x 18 mm in greatest dimensions. Cut surface was flat, pink, and fleshy. Sections were cut and stained with hematoxylin and eosin, the periodic acid-Schiff reaction, mucicarmine, and Wilder's reticulum stain.

Sections showed conjunctiva with marked reactive hyperplasia and widespread squamous metaplasia with acanthosis and papillomatosis of its epithelium (Fig. 2). Superficial stroma was dense with marked infiltration of lymphocytes and plasma cells, and many branching vascular channels with prominent endothelial cells were noted. The remaining stroma was myxomatous with many large fibroblasts, prominent blood vessels, and scattered chronic inflammatory cells (Fig. 3). In some areas, chronic inflammatory cell infiltrate surrounded the vascular channels, but in others the vessels were free of infiltration. Focal areas of unremarkable-appearing serous glands and ducts were seen (Fig. 4), and adipose tissue was present in deeper areas (Fig. 5). Special stains showed no mucosubstances and diffuse absence of a reticular skeleton.

DISCUSSION

A number of pathologic terms frequently confuse the nonpathologist. The term hamartia was derived from the greek verb hamartanein (to fail, err, or miss) by Albrecht (2) in 1904 to denote a "faulty mixture of ... normal [tissue] components." A hamartoma is a hamartia forming a tumorous mass. Histologically, it shows normal-appearing tissue proliferating in an area where it normally is found (e.g., a choroidal hemangioma). Chorista, and its tumorous counterpart choristoma, derive from the greek noun choristos (separation) and denote failure of separation of embryonal cells, thus causing proliferation of normal-appearing tissue in an area where it normally is not found (e.g., a choroidal osteoma). Note that a lesion that might be considered a hamartoma in one area of the body (e.g., a dermoid or dermal hamartoma in the subcutis) would be considered a choristoma in another part (e.g., a limbal dermoid or dermal choristoma).

Another confusing term is nevus, which is used in two different connotations. Most clinicians think of a nevus as a collection of pigmented "nevus" cells, a lesion which the pathologist terms a nevocellular nevus. The term nevus by itself refers to a lesion originating from embryonal cells and usually to a hamartoma found in skin. Jadassohn (3) originated the term organoid nevus to describe a faulty mixture of skin appendages. In 1932, Robinson (4) described a condition characterized by excessively large sebaceous glands as the nevus sebaceus of Jadassohn.

Nevus sebaceus of skin, a lesion frequently encountered clinically (5), has the distinctive histologic appearance of large numbers of mature and nearly mature sebaceous glands with reactive changes of the overlying epidermis. In addition, apocrine glands, often hyperplastic and cystic in appearance, frequently are seen deep to the masses of sebaceous gland nodules (6). A less common association was described in 1962 as the linear...
nevus sebaceous syndrome (1), a triad of midline facial skin lesions (nevus sebaceous of Jadassohn), seizures, and mental retardation. This has since been called by a number of alternate terms: organoid nevus phakomatosis, Jadassohn’s nevus phakomatosis, Feuerstein-Mims syndrome, Schim- melpenning-Feuerstein-Mims syndrome, as well as a change in spelling of the original term seba- ceus: nevus sebaceous syndrome and linear nevus sebaceous syndrome. The latter is the most common present usage. A name sometimes used, the epidermal nevus syndrome, was called an unfor-
Since the original description of the linear nevus sebaceous syndrome, neurological disorders, including cerebral and cerebellar hypoplasia and arachnoid cysts, have been reported (7). Other descriptions have included abnormalities of the skull and of the viscera (8). Of particular concern are reports of malignant neoplasms arising in the skin lesions, with basal cell carcinoma found in 15-20\% (5). Domingo and Helwig (9) reported aggressive-
appearing neoplasms in nine patients with nevus sebaceous of Jadassohn. Four were apocrine carcinomas (two of which had metastasized), three were pilar adnexal tumors, one was a squamous cell carcinoma (from which the patient had died), and one was an anaplastic complex adnexal and squamous cell carcinoma.

Ocular abnormalities have been found in 50% of cases (10); Alfonso and coworkers (11) found reports in 49 of the 70 cases they reviewed. These may include conjunctival lipodermoid choristomata, osseous choristomata of the choroid with subretinal neovascularization, angiomata of the orbit, and colobomata of the lids, iris, choroid, and optic nerve head (8,11-17). Other authors have found anophthalmia, microphthalmia, macrophthalmia, hemangiomata of the conjunctiva and sclera, and corectopia (18).

Many of these associated ocular findings are choristomata of variable composition. Choristomata often are classified pathologically into simple (single-tissue) and complex (multiple-tissue). Both of these types have been seen in the linear nevus sebaceous syndrome. Choristomatous lesions represented the third most common major group (22%) of a reported series of 282 epibulbar tumors in children (19); 6% of these choristomatous lesions were the complex variety. Combinations of hamartomata and/or choristomata of the central nervous system, skin, and eye have been classified under the broad term of phakomatoses. The term phakoma was first introduced by Van der Hoeve (20-21) to replace the term nevus. It derives from the greek noun phakes (lens-shaped or a birthmark). He described three neuro-oculocutaneous syndromes: angiomatosis retinae (von Hippel’s syndrome), neurofibromatosis (von Recklinghausen’s syndrome), and tuberous sclerosis (Bourneville’s syndrome), all of which feature multiple hamartomata. Since that time, other syndromes have been added to these, and linear sebaceous nevus syndrome has been included in these (13,22).

The most frequent ocular findings associated with the linear nevus sebaceous syndrome include conjunctival choristomata (11). There have been several recent reports describing these lesions. Wilkes et al. (8) described cartilage and islands of lacrimal tissue at the nasal corneoscleral limbus of their case. In addition, intrascleral cartilage and bone were seen. Lambert and colleagues (13) described focal conjunctival cartilaginous masses with interspersed small lacrimal glands.

The present case showed typical findings of the linear sebaceous nevus syndrome, including involvement of skin, central nervous system, and eyes. There were multiple facial hemangiomata and a huge, rapidly growing limbal mass, which, on pathological examination, was a complex epibulbar choristoma composed of myxomatous tissue containing ectopic lacrimal gland and adipose tissue. Overlying reactive changes included granulation tissue, chronic inflammation, and hyperplastic epithelium. The rapid growth of the lesion probably was because of these reactive changes, and the lack of recurrence may be related to the protection afforded by the tarsorrhaphy, and, perhaps, to scarring from the laser. While the complex epibulbar choristomata reported previously (8,11-17) have contained lacrimal, and adipose tissues, the unusually large size of the mass in our case and the myxomatous stroma we describe have not been reported before and are unusual features of this phakomatosis.

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Free Air in the Cavernous Sinus as an Incidental Finding

Jonathan C. Horton, M.D. Ph.D., Paul D. Langer, M.D., and Gary E. Turner, M.D.

Free air within the cavernous sinus was discovered incidentally on a computed tomographic (CT) scan. We suggest that air bubbles were introduced inadvertently when contrast material was injected just prior to CT scanning. On a repeat CT scan 16 days later, the air had disappeared.

Key Words: Cavernous sinus—Air bubble—Computed tomography.

A 50-year-old man sought evaluation in the ophthalmology clinic for long-standing, painless visual loss in the right eye. The visual acuity could be corrected to only 20/60. The right optic disc appeared pale and atrophic. A contrast-enhanced computed tomography (CT) scan was ordered to investigate the possibility of compression of the optic nerve by a tumor.

The patient was placed upon a gurney with the head of the stretcher elevated at 45°. An intravenous line was started in the right volar forearm and a bolus of 100 cc of iohexol contrast material (Omnipaque 300) was injected. Contiguous 1.5-mm axial CT images were subsequently obtained through the orbits and the perisellar region. The scan showed no abnormality of the globes or the optic nerves. The cause of visual loss in the right eye was never firmly established, but an old ischemic optic neuropathy was presumed to be responsible.

The remarkable finding on the CT scan was free air within the cavernous sinus. There were two circular bubbles located along the lateral wall of the right cavernous sinus (Fig. 1). The posterior bubble was slightly larger and nearer to the posterior apex of the sinus. It measured minus 373 Hounsfield units. On an axial section just below the bubbles, small irregular lucencies compatible with fat were
present within both cavernous sinuses (Fig. 1A, arrows).

On axial bone windows, the bubbles within the right cavernous sinus appeared isodense with air in the ethmoid and sphenoid sinuses (Fig. 2). No fractures of the bones of the orbits, sinuses, or cranium were seen.

To confirm our impression that the bubbles represented free air within the right cavernous sinus, the patient was rescanned 16 days later. On this occasion, no contrast agent was administered and no intravenous line was inserted. Matching contiguous axial CT sections were obtained (Fig. 3). The two bubbles within the right cavernous sinus were absent. The low-density structures consistent with fat, noted previously in each cavernous sinus, were unchanged in appearance (Fig. 3A, arrows).

**DISCUSSION**

On a CT scan obtained in search of an optic nerve tumor, we found two small, round, low-density areas within the right cavernous sinus. We interpreted these low-density areas as free air, based upon their appearance and their Hounsfield reading of minus 373 units. Small quantities of intracranial or intravascular air are rapidly resorbed by the body. The disappearance of the bubbles on the follow-up scan supports their identification as free air.

Lobules of fat are occasionally present within the cavernous sinus, and have been confused with free air (5). In our patient, small collections of fat were identified in each cavernous sinus (Fig. 1A, arrows). They were distinguished from air on the
basis of their greater density, irregular contour, and unchanged appearance on repeat scanning (Fig. 3A, arrows).

Free air in the cavernous sinus signifies a potential neurological or neurosurgical emergency. It has been reported as a sign of cavernous sinus thrombosis due to gas-forming organisms (1). Our patient was entirely healthy, so infection cannot be invoked as an explanation for the air in his cavernous sinus. Moreover, we were unable to elicit a history of recent sinusitis, trauma, flying, diving, or drug snorting or injection. It seems unlikely that air could pass directly from the contiguous paranasal sinuses through bone and dura into the cavernous sinus. It is equally improbable that air from an arterial source could reach the cavernous sinus after passing through the cerebral circulation.

We postulate that air bubbles, introduced along with contrast administration before the CT scan, may have traveled retrogradely up the internal jugular vein, petrosal sinuses, and into the cavernous sinus. Frequently, tubing is not purged adequately of small air bubbles before starting intravenous lines. Venous air bubbles normally pass via the right heart to the pulmonary capillaries, where they are trapped and absorbed. In this patient, we suspect that at the moment the air reached the right brachiocephalic vein, a well-timed cough or Valsalva maneuver propelled the bubbles into the internal jugular vein where they rose against the flow of blood.

Orrell and coworkers (6) reported a patient with septic cavernous sinus thrombosis and an air bubble visualized on a contrast CT scan. Hemophilus
influenza meningitis was diagnosed after examination of the cerebrospinal fluid. This organism does not form gas, leading the authors to speculate that the air entered the cavernous sinus from nose-blowing. In another recent case, Canavan and Osborne (3) found numerous air bubbles in the cavernous, straight, left transverse, and superior sagittal sinuses of a man who presented to an emergency room with right temporal headache from a decayed tooth. The patient had been flying earlier the same day in a hobby plane. Although he never exceeded an altitude of 6,000 ft, the authors attributed his intracranial air to barotrauma. We offer a new explanation for the air within the cerebral dural sinuses in these cases: iatrogenic introduction by intravenous injection prior to CT scanning. Our case serves as a caution that free air within the cerebral dural sinuses does not always represent a neuroradiological sign with grave implications. It may be nothing more than an artifact of CT scanning with intravenous injection of contrast material and air.

REFERENCES
Unilateral Conjugate Gaze Palsy Due to a Lesion of the Abducens Nucleus
Clinical and Neuroradiological Correlations

Genjiro Hirose, M.D., Ph.D., Kei Furui, M.D., Akira Yoshioka, M.D., Ph.D., and Koichiro Sakai, M.D., Ph.D.

We report a case of left-sided horizontal gaze palsy, ipsilateral adduction weakness, and left peripheral facial weakness, all of which indicate the lesion in the left median pontine tegmentum. The enhanced MRIs revealed a discrete left median pontine tegmental lesion, involving the abducens nucleus, MLF, and facial nerve knee. This lesion spared the area of the left PPRF. Among these structures, the area of the abducens nucleus seems to be responsible for the unilateral horizontal gaze palsy. We are not aware of any previous precise neuroradiological documentation of unilateral paralysis of conjugate gaze due to a lesion of the abducens nucleus by sagittal and horizontal MRIs.

Key Words: Horizontal gaze palsy—Abducens Nucleus—MRI—Paramedian pontine reticular formation (PPRF).

From the Department of Neurology, Kanazawa Medical University, Uchinada, Kahoku, Japan.

Address correspondence and reprint requests to Dr. Genjiro Hirose, Department of Neurology, Kanazawa Medical University, Uchinada, Kahoku, Ishikawa Pref., Japan. 920-02.

Paralysis of horizontal conjugate eye movements seen in patients with brainstem lesions is usually attributed to the involvement of the ipsilateral paramedian pontine reticular formation (PPRF), which is generally considered to be the pontine horizontal gaze center clinically.

However, considerable evidence suggested that the pontine lateral gaze center and the abducens nucleus might constitute a single anatomical structure (1, 2). Axonal transport techniques and physiological studies have indicated that the abducens nucleus contains motor neurons and internuclear neurons. The former innervate the ipsilateral lateral rectus muscle, and the latter, whose axons cross the midline and ascend via the contralateral medial longitudinal fasciculus (MLF), innervate the medial rectus subnucleus (3, 4). These studies indicate that ascending projections from abducens interneurons play a major role in conjugate horizontal eye movements. In spite of these experimental data, there have been few clinical examples supporting these data (5-8).

We report a case of unilateral horizontal gaze paralysis in whom the responsible lesion is restricted to the abducens nucleus as documented by magnetic resonance imagings with enhancement techniques and discuss the clinico-radiological correlation in this patient.

CASE REPORT

An 80-year-old woman was admitted to the hospital with a 1-day history of dizziness, double vision, and facial asymmetry. One day prior to admission she awoke with diplopia and drooping of the left side of her mouth. She could not close her left eye or gargle with water. Because of these
symptoms she was seen by a family doctor who referred her for further examinations. She denied other symptoms such as headache, nausea, or vomiting. She had been taking an oral antidiabetic drug with good control.

On examination, she was alert and oriented to three spheres. Cognition was quite appropriate. Her speech was mildly dysarthric due to left facial weakness. Her pupils were isocoric and reacted normally. She had a tendency to look to the right side. She had a complete horizontal palsy of saccades and pursuit eye movements to the left beyond the midposition (Fig. 1). Oculocephalic maneuver did not elicit eye movements toward the left. With the attempt to look to the right, her right eye abducted fully with a coarse horizontal nystagmus, and her left eye adducted incompletely, indicating a left internuclear ophthalmoplegia. The return eye movement from the right extreme position to the midline was preserved with slow saccades. Convergence was present. She had left upper and lower facial weakness; taste was preserved. The rest of the cranial nerves were normal. She had no limb weakness. Pain and temperature sensation were normal in her limbs and her trunk. Her deep tendon reflexes were normal and no cerebellar signs were noted. The plantar response was equivocal on the right side. A left lower pontine medial tegmental lesion was diagnosed.

Serial CT scans with enhancement were all reported negative. MRI 2 weeks after admission revealed a discrete high-signal lesion in the area of the medial lower pontine tegmentum on the left side by the T2 (TR:2,500, TE:90) images. This lesion was not noted by the T1 images (Fig. 2A,B). The lesion was enhanced by Gd-DTPA (Fig. 3A-C). This lesion gradually reduced in size on MRI 6 weeks later (Fig. 3D). These neuroradiological findings favor the diagnosis of ischemic infarction rather than hemorrhage or hemorrhagic infarction.

**FIG. 1.** Extraocular movements of the patient on admission. Complete horizontal gaze palsy to the left beyond the midposition is noted with incomplete adduction of the left eye.
The left adduction weakness disappeared within 10 days after admission with a gradual recovery of the right adduction weakness next. At this stage she still had a left lateral rectus muscle weakness, and this cleared completely within about 2 months. Her left facial muscle weakness cleared last, after 3 months.

AC and DC electro-oculographic (EOGs) recordings on hospital day 50 revealed incomplete slow saccadic eye movement toward to the left side and
saccadic eye movements toward the right in the eye tracking test. The optokinetic nystagmus (OKN) with quick phases to the patient's left was grossly defective when a drum rotated from left to right (Fig. 4).

**DISCUSSION**

Lesions in the abducens nucleus produce paralysis of the ipsilateral lateral rectus muscle and a paresis of contralateral ocular adduction on attempted horizontal gaze toward the side of the lesion. This symptomatology is quite different from the ipsilateral lateral rectus weakness secondary to the lesion in the abducens nerve fascicle, which is far more common. Carpenter and his associates (1) reported that the lesion strictly confined to the abducens nucleus showed an ipsilateral conjugate gaze palsy, involving the ipsilateral lateral rectus and contralateral medial rectus muscles in monkeys. Since then, considerable evidence suggests that the pontine center for lateral gaze and the abducens nucleus may constitute a single anatomical structure. Axonal transport techniques and physiological studies have indicated that the abducens nucleus contains motor neurons that innervate the lateral rectus muscle and internuclear neurons, which cross the midline, ascend via the contralateral MLF, and innervate the oculomotor nucleus (2-4). From these data, the paresis of contralateral ocular adduction, which is seen in the paralysis of lateral gaze and the paresis of ipsilateral adduction in anterior internuclear ophthalmoplegia are now believed to result from the involvement of abducens internuclear neurons or their ascending axons.

In our patient, neurological deficits consist of left-sided horizontal gaze paralysis, adduction weakness of the left eye and left-sided peripheral facial nerve palsy. These deficits were interpreted that this patient had left-sided gaze palsy and an internuclear ophthalmoplegia on the same side ("one and a half" syndrome) with the left peripheral facial nerve palsy. All of these symptoms indicate the lesion in the left median pontine tegmentum. This site of involvement was confirmed by the T2-weighted MRIs and gadolinium-enhanced MRIs. The lesion seen on MRI involved the abducens nucleus, facial nerve nerve, and MLF on the left side, explaining the patient's signs. There is a possibility that the PPRF might be also involved in our case. But PPRF is anatomically situated near the midline and ventrally to the MLF between the abducens and trochlear nuclei. It was not seen to be involved in the MRI of our patient (Fig. 3). Bronstein et al. (8) reported MRI findings in seven patients with unilateral gaze palsy, but

![FIG. 4. Optokinetic nystagmus (OKN) recordings on the 50th day of the illness. The notation Right OKN refers to a stimulus which normally induce OKN to the patient's right side, actually the drum rotated around the patient with stripes passing from the right to the left. Left OKN refers to the OKN, when stripes pass from the patient's left to the right. SP Velocity indicates the slow phase velocity, and an upward and downward deflection of the EOGs denotes an eye movement to the right and the left, respectively. Calibrations are shown by vertical bars.](https://example.com/fig4.png)
only one of those had a localized lesion in the abducens nucleus secondary to a small hemorrhage. Even in this case, only the horizontal image was analyzed for localization.

According to Pierrot-Deseilligy, horizontal gaze palsy secondary to the lesion in the paramedian pontine reticular formation, which he designates as the “Pontine reticular formation syndrome,” is different from the syndrome due to the lesion in the abducens nucleus. In the PPRF syndrome, all ipsilateral saccades, including voluntary saccades and quick phases of nystagmus as well as the return phase of the contralateral hemifield eye movement are diminished. In our case, the return movement from the right abducted position to the midline was well preserved, supporting the MRI evidence that responsible lesion was in the abducens nucleus.

As for the etiology of our case, her clinical symptoms and hospital course with complete clearing of the symptoms favor the diagnosis of ischemic cerebrovascular disease secondary to the occlusion of the paramedian perforating artery of the pons.

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Quantitative Longitudinal Assessment of Saccades in Huntington’s Disease

Allen J. Rubin, M.D., W. Michael King, Ph.D., Kirk Alan Reinbold, M.S., and Ira Shoulson, M.D.

While participating in a controlled study of baclofen as protective therapy, 39 Huntington’s disease (HD) patients underwent measurements of horizontal saccade latency and velocity, repeated longitudinally over a 2-year period. Significant worsening of saccade latency and of mean velocity was detected in untreated patients. Although individual variation was great, initial velocity impairment was found to be more prominent in younger patients. Factors are identified that may affect the rate of decline in supranuclear oculomotor function, including age and the severity of illness at the time of initial assessment. We propose that serial quantitative measurement of saccade performance is a useful clinical marker of the rate of disease progression against which the efficacy of treatments may be tested.

Key Words: Huntington chorea—Saccadic eye movements—Movement disorders.

Slowing of saccades in Huntington’s disease (HD) has been reported as an early clinical feature useful in detecting onset of illness (1–3), described qualitatively, and shown to progress as a feature of advancing disease (4). Quantitative studies have shown that early age of onset of HD is associated with increases in horizontal saccade latency and decreases in velocity (5), but quantitative measures of the rates of decline in saccadic latency and velocity have not been established. Using a technique of oculomotor measurement that is noninvasive and readily accessible in a clinical setting (6), we seek to establish the rates of change of saccadic performance by serial quantification. We propose that this technique provides a neurophysiologic marker of disease progression. The reliability of such a marker for longitudinal study, in contrast to clinical examination of oculomotor or other motor systems, would derive from the intrinsic regularity in the performance of brainstem saccade generators. Except for minor spontaneous variations in performance (7), the saccadic system assessed in standardized test conditions is expected to provide the regularity of performance required for quantitative longitudinal analysis.

SUBJECTS

We measured horizontal saccade performance in patients who participated in a double-blind placebo-controlled study of baclofen as protective therapy in HD (8). Of 39 patients tested longitudinally, 17 were on placebo, and an additional 7 pilot study patients were followed whose treatment status remains unknown. All patients were recruited while in early stages (I and II) of disease (Shoulson-Fahn Total Functional Capacity (TFC) scale > 6) (9,10), and in most cases were tested yearly over the course of the study. The initial test occurred at
a mean 17.1 months after recruitment (range: 6–24 months). Paired quantitative comparisons of saccadic performance over a 2-year interval were achieved in 39 patients for most variables. In the data presented, missing values account for instances in which total sample size is reported to be <39. For the sample, the age of onset of HD symptoms was 34.7 ± 10.7 years (mean ± SD), and age at the time of our first assessment was 42.2 ± 10.1 years. Duration of illness was 8.1 ± 3.4 years, mean ± SD. TFC scores, as averaged among seven independent observers, ranged from 13 to 6 (mean 10.0 ± 1.7 SD) when patients were initially tested. TFC scores progressed in a 2-year interval to range from 12.8 to 2.8 (mean 8.3 ± 2.2 SD), encompassing functional Stages I–IV of disease.

Because baclofen, a GABA analog, is clinically active in ocular motor systems (11), and the related GABA neurotransmitter system is physiologically involved in the premotor system for saccade generation (12), patients receiving baclofen were treated separately for analysis. In all cases, we have compared the rates of progression in eye movement measures over a 2-year epoch following randomization, avoiding the comparison of eye movement parameters between the premedication baseline and later measurements while on medication. This confines our inference for medicated patients to rates-of-change over time, controlling for direct drug effects on latency and velocity. Patients randomized to placebo were not permitted any psychoactive medication unless seriously disabled by movement or depression. None of the patients tested were treated with neuroleptics.

METHODS

Horizontal eye position was recorded by an infrared reflectance technique with 0.25° resolution (Gulf & Western Eyetrac Model 200). While abnormalities in saccades in HD may occur with more severe vertical than horizontal impairment (4), measurement of horizontal saccades with the infrared technique avoids the relative inaccuracy caused by the interference of the lid in vertical measurement, a potentially significant problem in HD patients who typically show an increased rate of blinking and blink-saccade synkinesis (13,14). Blink artifact was monitored independently by vertical DC electro-oculogram; saccades associated with blinks were excluded from analysis. System bandwidth was DC to 50 Hz. Testing was performed in the dark in a perimetric field, the equidistant targets viewed monocularly. The head was secured against both chorea and gaze-driven head movements in a stabilizing chin-forehead mount.

Targets for saccades were red LEDs subtending 0.5° visual angle, placed perimetrically at 5° intervals eliciting saccades ≤40° in amplitude, and presented in pseudorandom sequence after unpredictable delays. All fixation targets were within 20° of primary gaze. Saccades of greater amplitude than 20° were therefore stimulated by peripheral targets.

Eye position signals were displayed by chart recorder (Grass Model 78B polygraph) running at 60 mm/s for maximal resolution. Polygraph recordings of eye position were quantified by use of a digitizing pad (GTCO Digipad-5) operating with a LSI 11/23 computer. Eye velocity signals developed via analog differentiation were also monitored by polygraph display to improve visual resolution of onset and endpoints of the saccade epoch. For each saccade, the latency from target change, the total saccade duration, and the amplitude were derived. Such direct reading of eye movement records by visual inspection has provided consistent results by others (15). Typically, 80–120 saccades were analyzed for each patient.

Summary measures were developed to characterize the saccade latency and velocity performance by an individual at each point in time. Latency is the interval (in milliseconds) from the unpredictable target change to the onset of saccadic eye movement; a mean latency for all saccades served as the summary measure. As saccade velocity varies with amplitude, we required a single value to characterize the velocity performance and allow comparison between patients who may make a paucity of saccades of a given amplitude, and allow comparisons over time. We calculated mean velocity (MV) for each saccade before any hypometric corrections, representing the duration of the total saccade divided by the total saccade amplitude, MV = amplitude/duration, and from the entire sample of saccades derived the amplitude-duration relation. This relation is adequately described by a linear equation (15). We extrapolated from this regression the velocity intercept for a 30° amplitude, designated as "projected mean velocity" (MVp). This projected measure (MVp) is highly correlated (r = 0.88, p < .001), with the mean for each patient of actual MV of all saccades of amplitude 30° ± 5° taken together, supporting that this measure adequately describes the actual velocity performance. Linear regressions were not accepted for a patient if variability within a test performance yielded an amplitude-velocity correlation of less than 0.5.

Published normal ranges for this measure would lead to expected MVp = 270–375°/s (15). Compa-
rable results were achieved using our methods in 29 normal controls showed a sample mean $MV_p = 249 \pm 8$ (mean $\pm$ SEM, range: 175–323). When we divide normal controls according to the median age (42) for HD patients, we note that older controls showed a mean $MV_p = 258 \pm 10$, and younger controls showed mean $MV_p = 238 \pm 13$.

The precision of visual inspection of a polygraph record for determining saccade duration was validated at the last visit of most patients. Redundant recording in both polygraph and computer-digitized modes was available for a subset of 34 HD patients. (This instrumentation was not available, however, for the earlier longitudinal testing.) The visual inspection method was compared to velocity analysis in which both average and peak velocity were detected by a quantitative criterion. The choice of the end of the saccade on which the denominator of MV (saccade duration) is highly dependent, could be defined uniformly in computerized analysis as the point at which saccade velocity returned to a value 5% of the peak velocity. The correlation for $MV_p$ between the methods was $r = .84$ ($p < .001$).

A physiologic relation between mean velocity and peak velocity is well recognized (15,16), providing the basis for further validation of our method. Saccade peak velocity (digitally derived), which is independent of the endpoint of the saccade, is also highly correlated with $MV_p$ (derived by visual inspection) in 34 HD patients ($r = .78$, $p < .0001$), and with $MV_p$ (digitally derived) ($r = .81$, $p < .0001$), where measures were developed redundantly in the same test performance. $MV_p$ is therefore correlated with a value extrapolated from the saccade “main sequence” (17). Assessment of reliability of $MV_p$ is approximated by comparison of test-retest values obtained in a subset of patients free of medication separated by the short interval of only 6 months. Mean velocity measures correlated significantly ($r = .94$, $p < .01$, $n = 4$) between test and retest. Latency measures also correlated significantly ($r = .86$, $p < .005$, $n = 6$) in this short interval.

**RESULTS**

The ability of some patients to generate saccades of large amplitude, which we define uniformly as those of $\geq 26^\circ$, was affected selectively over a 2-year interval. In our study, 11 patients had asymmetric dropout of large saccades in one direction compared to their own performance on the same test 2 years earlier, and 3 more patients had complete dropout of large saccades, meaning that they could not generate any saccades of amplitude $\geq 26^\circ$. As our measure of latency was affected by this selective dropout, we report longitudinal latency data for 25 patients whose capacity for generating large amplitude saccades was comparable over the 2 years. In a 2-year interval, significant worsening was detected in these HD patients of mean saccade latency, both in placebo and in baclofen-treated groups (Table 1).

Approximate rates of change are estimated from the differences in group means over 2 years. In the placebo group, an 8% per year increase was measured in mean latency of all saccades (paired $t$, $p < .01$). When we select a subset of large saccades, we find a 13% increase per year in large saccade mean latency ($p = .05$), and greater departure from the normal value of 208 $\pm$ 5 (mean $\pm$ SEM) obtained in 29 normal controls. These rates appeared higher in the patients randomized to the treatment group, increasing by 19% ($p = .001$) and 22% ($p = .005$) per year, respectively. Although at the first measurement there was little difference between the mean latency for all saccades and large saccades, latency was increased to 279 $\pm$ 71 (all saccades)

<table>
<thead>
<tr>
<th>TABLE 1. Saccade latency</th>
<th>Mean $\pm$ SD (ms)</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Baclofen</strong></td>
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<tr>
<td>Latency in all saccades increases significantly in 2 years</td>
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<tr>
<td>At first test</td>
<td>223 $\pm$ 44</td>
</tr>
<tr>
<td>2 years later</td>
<td>259 $\pm$ 36**</td>
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<tr>
<td>N = 11</td>
<td>N = 8</td>
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<tr>
<td>Latency in large saccades (amplitude $\geq 26^\circ$) shows relatively greater rate of increase</td>
<td></td>
</tr>
<tr>
<td>At first test</td>
<td>253 $\pm$ 86</td>
</tr>
<tr>
<td>2 years later</td>
<td>317 $\pm$ 73*</td>
</tr>
<tr>
<td>N = 11</td>
<td>N = 8</td>
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Paired $t$-test comparing first test to that 2 years later ($^*p < .05$, $^{**}p < .01$, $^{***}p < .001$). Differences between placebo- and baclofen-treated groups at a given time are not significant. Combined group includes HD patients from pilot studies whose treatment status with respect to baclofen is unknown. Normal mean latency does not differ for small and large saccades: 208 $\pm$ 5 ms (mean $\pm$ SEM) in 29 controls.
and to $314 \pm 67$ ms (subset of large saccades only), greater than 100 ms above the normal value after 2 years. No association with the progressive impairment of latency was detected related to age, age of onset, or to duration of illness. Unexpected observations are made, however, that in some HD patients saccade latency often increases with saccade amplitude, a relationship rarely present in controls. In addition, prolongation of latency may occur asymmetrically, varying between saccades directed leftward or rightward.

Similarly, in a 2-year interval significant worsening was detected in HD patients of saccade $MV_p$ both in placebo and in baclofen-treated groups. For HD patients the sample mean $MV_p$ was $178 \pm 52^\circ/s$ declining over 2 years to $153 \pm 45^\circ/s$ (range: $40-250^\circ/s$). Missing data were encountered less frequently because estimates derived from linear regression were still obtainable despite dropout of saccades of large amplitude.

The rate of $MV_p$ decrease is approximately 6% per year in nonmedicated patients (paired $t$ test, $p = .02$), and 10% per year in patients in the treatment group (paired $t$ test, $p = .009$). Overall, in a sample of 38 HD patients an average 7% per year decline in saccade velocity is demonstrated (paired $t$ test, $p = .0002$). These values are shown in Table 2.

**AGE EFFECTS ON SACCADE VELOCITY**

We and others (5,18) have reported previously that saccadic velocity defects in early stages of HD are less prominent with later age of onset. In this study, impairment in saccadic velocity is directly related to functional measures of disease progression (TFC). As shown in Fig. 1, mean saccade velocity ($MV_p$) declines with progression of disease. Each of 38 HD patient's $MV_p$ in degrees per second is plotted against the mean TFC score obtained from 7 observers. Figure 1 also illustrates the effect of age by coding for four quartiles of age. The oldest quartile are least impaired in saccade velocity, and do not show a decline in velocity with progressive lose of functional capacity (TFC). A regression line highlights the direct relation between functional capacity and saccade velocity that hold for the other three quartiles, and yields a correlation of $r = .48$, $p < .01$. Illustrated as well is the observation that for patients in Stages I and II of illness (i.e., TFC >6), saccade velocity often falls within the range of normal, and that this is more likely in the older patient. In this sample of early patients, age of onset was strongly associated ($r = .95$) with age and did not provide any additional explanatory potential.

In Fig. 2 we plot the $MV_p$ for each HD patient against age, at the time of his first test and again 2 years later. For the whole sample there is an inverse relation of saccade velocity to advancing age (regression line). This demonstrated a comparison between groups of patients whose ages differ by decades. Individual to individual variation is great within any age group. Superimposed on this trend, distinct short-term losses in velocity over a 2-year epoch is apparent for many patients, sufficient in degree to account for the finding of significant longitudinal decline in velocity over time for the HD sample as a whole.

An alternative illustration of rates of change in velocity is provided in Fig. 3, where $MV_p$ at the time of the first assessment is plotted against $MV_p$ as assessed 2 years later. Here the diagonal represents no change, individuals falling above the diagonal have shown small increments in velocity, and those falling below the diagonal demonstrate decrements in velocity over time. Individuals are coded in the figure for age, showing a possible trend that younger patients manifest greater velocity impairment, but that the rate of velocity decline (fall-away from the diagonal) may be greater in the older patients. Rate of decline is compared by age quartiles in Table 3. Differences attain or approach statistical significance within a 2-year epoch for the older two quartiles (mean 40 ± 48^\circ/s decline) com-

**TABLE 2.** Saccade mean velocity ($MV_p$) decreases significantly in 2 years

<table>
<thead>
<tr>
<th>Age Quartile</th>
<th>Mean ± SD (°/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Baclofen</td>
</tr>
<tr>
<td>At first test</td>
<td>181 ± 51</td>
</tr>
<tr>
<td>2 years later</td>
<td>158 ± 39</td>
</tr>
<tr>
<td>N = 17</td>
<td>N = 15</td>
</tr>
</tbody>
</table>

**TABLE 3.** Severity of saccade mean velocity ($MV_p$) slowing and rate of decline is compared among age quartiles

<table>
<thead>
<tr>
<th>Age Quartile</th>
<th>At first test</th>
<th>Two years later</th>
<th>Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>N</td>
<td>Mean ± SD (°/s)</td>
<td></td>
</tr>
<tr>
<td>24–35</td>
<td>8</td>
<td>130 ± 43</td>
<td>136 ± 49</td>
</tr>
<tr>
<td>36–41</td>
<td>11</td>
<td>152 ± 39</td>
<td>139 ± 35</td>
</tr>
<tr>
<td>42–51</td>
<td>9</td>
<td>172 ± 43</td>
<td>155 ± 33</td>
</tr>
<tr>
<td>52–66</td>
<td>10</td>
<td>202 ± 47</td>
<td>187 ± 38</td>
</tr>
</tbody>
</table>

**TABLE 3.** Severity of saccade mean velocity ($MV_p$) slowing and rate of decline is compared among age quartiles

$^*$p < .05, **p < .01, ***p < .001. Differences between placebo- and baclofen-treated groups at a given time are not significant. Combined group includes HD patients from pilot studies whose treatment status with respect to baclofen is unknown.
SACCADES IN HUNTINGTON'S DISEASE

Compared to the younger two quartiles (17 ± 32%/s decline).

**DISCUSSION**

While it is recognized that supranuclear oculomotor defects occur in HD and progress with advancement of disease, we have demonstrated that significant decline can be quantified in a relatively early HD sample in a 2-year epoch. Incremental change in latency was measured in 88% of patients, and decremental change in velocity measured in 72%, this degree of abnormal change achieving statistical significance for both measures. While progressive impairment was not detected in every patient, such a measurement may represent a marker of neurodegeneration against which to test the success of protective therapeutic interventions in clinical trials, for example, those built on treatment strategies that modify putative excitotoxic mechanisms of neuronal loss (19-21). The ability to detect significant change in a 2-year epoch, makes this technique practical for application in clinical drug trials. The addition of well-defined quantitative biological markers to clinical rating scales for disease progression, presents an opportunity to increase statistical power in clinical trials in HD. Noting that many patients in Stage I and II of disease will have saccade velocities within the normal range, an electrophysiological decline may be nevertheless detectable, which presumably may be undetectable by clinical observation alone. The electrophysiological measurement of saccadic eye movement therefore adds an important complement to clinical observation in the tracking of HD progression. While the impairment of supranuclear saccadic dysfunction in HD is not localized to a specific region of neuropathological involvement (22), measurement of saccade generation may represent a strategy for detecting and tracking involvement (either degenerative or neurochemical) in subsystems in basal ganglia circuits for eye

**FIG. 1.** Total functional capacity declines with loss of saccade velocity. Effects of age are illustrated by dividing the HD patients into four age quartiles: O, ages 24-35; ●, ages 36-41; □, ages 42-51; and ■, ages 52-66. In the oldest quartile, no relation of TFC to MVₚ appears to hold. A dashed regression line (A) illustrates the relation of TFC to MVₚ for the other three quartiles. Comparable normal MVₚ values are 238 ± 13 (mean ± SEM) for ages below the median age of 42, and 258 ± 10 above the median age.

**FIG. 2.** Change in mean saccade velocity (MVₚ) is illustrated over a 2-year epoch for each HD patient, plotted against the age of the patient. O, placebo-treated patients; ■, baclofen-treated patients. A dashed regression line illustrates the inverse relation of saccade velocity to advancing age for the entire sample (r = .46, p < .01).
movement control, or projections to brainstem premotor systems (23, 24).

In addition to measurements of the rates of decline, a number of specific observations have emerged regarding the natural history of saccade latency and saccade velocity in HD. Changes in latency were more detectable by the selective observation of large saccades, suggesting a greater sensitivity of this measure. Similarly, both in testing and clinically, some patients exhibited a selective dropout of large saccades with passage of time, particularly patients who had greatly slowed saccade velocity. This observation implies that the supranuclear saccadic disturbance of HD may apply earlier to saccades of large amplitude. Indeed, three patients with slowed velocity had complete dropout of large saccades after a 2-year interval as to obviate our capacity to make a quantitative interval comparison. We also noted that early patients were often asymmetrically impaired, showing differences by direction of saccadic refixation, and that this asymmetry persisted over time. In contrast, this asymmetry occurred less commonly in patients with advanced impairment of saccade velocity. Separating saccades by direction of refixation may augment sensitivity for detecting progression in early disease.

Review of technical aspects of this study provides direction for improving future longitudinal studies. In an apparent paradox, some untreated patients showed modest improvement in velocity measures. This occurrence has questionable face validity in a progressive degenerative disease, and may be due to measurement error, to spontaneous variations in motor activity, or to circumstantial differences in each testing session, such as degree of alertness. An alternative technical explanation of this apparent paradox is offered as well. An estimate, such as $MV_p$, which relies on linear regression is biased by the selective dropout of large saccades to weight regression heavily on small saccades, and may overestimate a projected intercept for a large amplitude. The bias deriving from dropout of large saccades may be averted by referring comparisons to a less eccentric amplitude as the linear intercept. While hand-digitized analysis of polygraph records of eye position was adequate for this present analysis, there would be an advantage in computerized techniques that derive saccade measures by uniform criteria, or provide detection of the absolute peak saccadic velocity. These techniques may offer advantages in reliability for longitudinal assessment.

In the report of the clinical trial of baclofen, from which this sample of HD patients was drawn, a rate of TFC decline per year was reported of $0.53 \pm 0.46$ units per year on a 13-point scale, representing $4.1 \pm 3.5\%$ decline per year. This resembles closely the magnitude of progression of impairment we have described in saccade latency and in velocity. It was recognized that the baclofen-treated patients in this study were not randomized with respect to mode of inheritance, and showed a 2:1 ratio of paternal:maternal inheritance. As we have detected more rapid rates of progressive impairment in both saccade latency and velocity in the baclofen-treated sample, we may conjecture that this effect may relate to cumulative treatment effects of medications active in the oculomotor system, to effects of mode of inheritance, or to the interaction of medication with the rate of progression of the underlying disease.

Although age and age of onset were strongly correlated in this sample, an interaction may be
present between age of onset and duration of illness ($r = -.33, p < .06$), sufficient to introduce a bias that younger and earlier onset patients have manifested illness for a longer period at the time of testing. This interaction, or the finding of generally lower TFC ratings in the younger patients, may indicate a floor effect ("burnout") for saccadic function in the patients with earlier onset and longer duration of illness. The floor effect may be present despite the controlling strategy that the study as a whole recruited patients restricted to early functional stages of disease. This interaction may account for the apparent conflict with recent studies establishing a more rapid rate of disease progression in patients with early age of onset, as measured neuropathologically (25,26). While we have confirmed an overall inverse association between age and saccadic velocity, the appearance of a relative damping of the rate of decline of saccade velocity in younger patients required control for duration of illness.

Within the oldest quartile of patients, a subset of patients has relative preservation of saccade velocity or has a slower rate of decline of velocity over a 2-year interval. A reduced degree of motor dysfunction in the elderly-onset HD patient, perhaps excepting chorea, is asserted by some authors (25,27). The recognition in this sample of older patients whose total functional capacity declined despite preservation of saccade velocity, may imply that functional impairment was arising in these patients from other aspects of the disease, such as cognitive or emotional disturbances. Alternatively, eye movement disturbance may fail to reflect the degree of overall motor impairments in these patients.

In summary, our study establishes the utility of quantitative longitudinal assessment of saccade latency and velocity for assessing the progression of Huntington’s disease over a period of 2 years. Patients with less prominent eye movement impairment initially may appear to have a more rapid rate of measurable progression of their oculomotor dysfunction. This observation may derive from the age-effect of less impairment in patients with later age-of-onset, or may derive from the floor effect, where change is less detectable in patients with relatively severe impairment initially. We have found for saccade latency that the measurement of changes in saccades of large amplitude may be more sensitive, and for saccade velocity that the loss of the capacity to make large saccades in patients with slowed velocity may be a measure itself of disease progression. Longitudinal research design in HD should anticipate marked individual variation, effects of age of onset, and variation of rates of change attributable to the severity of illness at the time of initial assessment.

Acknowledgments: Appreciation is expressed to Kathleen Gala, Allen D. Pettee, and Christopher R. Thorp for technical assistance.

REFERENCES
A Comparative Study of Tear Secretion in Blepharospasm and Hemifacial Spasm Patients Treated with Botulinum Toxin


In the neuro-ophthalmology clinic at St. Vincent’s Hospital, Melbourne, 57 patients with blepharospasm and 50 patients with hemifacial spasm were treated with botulinum toxin. Schirmer tear tests were conducted on all the patients prior to each treatment and at 1 week following treatment where possible. The results were compared with a control group of 107 patients selected by age and sex. The blepharospasm patients were found to have a significantly lower tear secretion than that of the control group, using the Mann-Whitney test (median = 3.5 mm, compared with median = 11.0 mm, p < .0001). This did not improve following treatment. The patients with hemifacial spasm did not have significantly different tear secretion from that of the control group (t = 1.0, p > .05). To investigate whether there was any relationship between the symptoms and the result of the Schirmer test, a survey was also conducted on the patients with blepharospasm and hemifacial spasm regarding symptoms, frequency, and type of drops/ointment used.

Key Words: Dry eye—Schirmer Tear Test—Botulinum toxin—Blepharospasm—Hemifacial spasm.
Several methods of measuring tear secretion have been described previously (17–21) and it is the aim of this study to investigate tear production in patients with blepharospasm and hemifacial spasm using the Schirmer tear test and to correlate any symptoms they may have with the Schirmer test measurements.

MATERIALS AND METHODS

At St. Vincent’s Hospital, Melbourne, 107 patients, 57 with blepharospasm and 50 with hemifacial spasm, were treated with botulinum toxin. A total of 429 treatments were given with a mean follow-up of 16.5 months (range 0.6–32.8). A control group consisting of 107 patients selected by age, sex, and informed consent had their tear secretion measured using the Schirmer tear test. These patients were selected from a general ophthalmic practice and were not excluded or included because of their ocular condition unless it was physically impossible to conduct the test (e.g., the presence of a lid lesion, sutures, etc.). The Schirmer test was performed according to the directions provided. That is, the test was performed before any topical medication was given and without local anaesthetic. The rounded tips were bent at right angles and were placed in the lower fornix of the eye. The patients sat with their eyes closed for 5 minutes. The test was performed by the same person each time. Similarly, all the blepharospasm patients and hemifacial spasm patients had their tear production tested with the Schirmer test strips prior to each botulinum treatment and at 1 week following the initial treatment when possible; however, since some patients were country, interstate, or elderly, not all of them had the Schirmer test performed at 1 week post-treatment.

For the majority of patients (102/107), a survey was also conducted to establish what symptoms
were complained of and the frequency and type of drops or ointment that were used and whether they provided any relief. All data from the Schirmer test measurements and the dry eye survey were entered onto a data base and analysed using the Minitab statistical program in consultation with Melbourne University Statistical Consulting Centre.

RESULTS

The mean age of the patients who received botulinum toxin was 63.0 ± 12.1 years, and the mean age of the control group was 64.4 ± 10.4 years. This was not significantly different using the two-sample t test (t = 0.9, p > .05). The ratio of females to males in the control group was 2.0:1, in the blepharospasm group was 2.3:1, and in the hemifacial spasm group was 2.7:1. There was no significant difference in the Schirmer test results for females and males in any of the groups.

The mean Schirmer result for the control group was 13.4 ± 10.0 mm compared with 7.9 ± 8.9 mm for the blepharospasm group (see Figs. 1 and 2). When compared statistically, there was a significant difference between the blepharospasm group and the control group using the Mann-Whitney test (median = 3.5 mm compared with median = 11.0, p < .0001). There was no significant difference between the hemifacial spasm group (mean = 12.2 mm, SD = 10.0) and the control group (t = 1.0, p > .05). When the Schirmer readings were compared for the affected and unaffected eyes in the hemifacial spasm patients, there was no significant difference in the measurements. The mean Schirmer measurement for the affected eye was 12.2 ± 9.6 mm and for the unaffected eye was 12.2 ± 10.6 mm (t = 0.01, p > .05).

The results of the Schirmer test were divided into three separate groups: 0 to <5 mm, 5 to <10 mm, and those who had a Schirmer measurement of ≥10 mm. Using the chi-square test, there were significantly more patients with a measurement of <5 mm in the blepharospasm group (56%) than in the control group (21%) (X² = 20.1, p < .0001). However, there was no significant difference between the control group and the hemifacial spasm group (26%) (X² = 0.6, p > .05) (see Figs. 3-6).

The Schirmer measurements for the blepharospasm patients did not improve following treatment with botulinum toxin. The pre-treatment measurement was 7.9 ± 8.8 mm compared with the post-treatment measurement of 9.2 ± 7.0 mm, p > .05. The t test on the difference between the pre- and post-treatment Schirmer measurements was not significant (t = 1.4, p > .05).

The Schirmer results for 22 blepharospasm patients (44 eyes) who had 5 or more consecutive Schirmer tests were compared to investigate the reliability or variability of the Schirmer test. The mean and standard deviation for each eye was calculated and plotted. This showed that the variabili-
ity appeared to be related to the magnitude of the measurement, that is, the larger the average Schirmer measurement, the larger the variability.

The average standard deviation for the 44 eyes that had repeated measurements was ±3.5 mm. However, when the measurements were divided into 3 groups, the standard deviation increased with the larger measurements. Therefore, with an average Schirmer measurement over 5 or more consecutive tests you could expect a standard deviation of ±2.18 mm if the average measurement was <5 mm and as much as ±7.23 mm if the average measurement over the 5 or more tests was greater than 10 mm (see Table 1).

Of the 56% of blepharospasm patients with a Schirmer's measurement of less than 5 mm, 50% complained of dry eye, 40% felt they had no symptoms, 7% did not complete a form, and 3% complained of watery eyes (see Fig. 7).

In the 30 blepharospasm patients who had dry eyes, 11 of them used tear substitutes on a regular basis; 82% of those using drops complained of dry eye, and the remaining 18% had no symptoms or complained of a watery eye. Several types of tear substitutes were used in varying amounts to provide relief of symptoms.

**TABLE 1. The average standard deviation for Schirmer measurements with repeated testing**

<table>
<thead>
<tr>
<th>Group (average reading for each eye after repeated testing)</th>
<th>Average SD for each eye after repeated testing</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;5 mm</td>
<td>±2.18 mm</td>
<td>30</td>
</tr>
<tr>
<td>5 to &lt;10 mm</td>
<td>±5.18 mm</td>
<td>8</td>
</tr>
<tr>
<td>≥10 mm</td>
<td>±7.23 mm</td>
<td>6</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Diminished tear secretion was found in patients with blepharospasm. It is not known whether the reduction in tear secretion is one of a number of factors that may play a part in the causation of blepharospasm. Unfortunately, treatment with botulinum toxin did not improve tear function, nor did the use of tear substitutes cause the blepharospasm to diminish.

The lack of improvement in tear secretion with effective treatment for the blepharospasm would suggest that either this is an underlying condition that persists or the defective tear secretion is related to the defective lid closure. Although the botulinum improves the blepharospasm, it does not improve the physiology of the blink reflex to increase tear secretion back to normal. Furthermore, if the reduced tear secretion was due to the abnormal lid closure, one might expect that with the
hemifacial spasm patients there would be reduced tear secretion in the affected eye, and this was not the case.

As we were unable to demonstrate any improvement in the blepharospasm with the use of artificial tears, we concluded that these patients with reduced tear secretion, who are asymptomatic, probably do not need tear substitutes, as this may result in a low compliance rate.

CONCLUSION

The blepharospasm patients were found to have dry eyes when compared with the hemifacial spasm patients and the control group. This did not improve when the blepharospasm was treated with botulinum toxin and may indicate that the dry eyes could be a predisposing factor, along with others, to developing blepharospasm rather than as a result of the abnormal lid closure. The investigation of symptoms also shows that not all patients who demonstrate dry eyes on the Schirmer test necessarily complain of dry eyes. The variability of the Schirmer test with repeated testing appeared to be related to the average size of the measurement. The larger the measurement, the larger variation you could expect with a repeated measurement.

REFERENCES


This excellent book details with astonishing clarity how to evaluate and work up almost any emergency ophthalmologic complaint or condition one can imagine. It begins with a thorough chapter on how to perform a good eye history and examination. Next is a very complete chapter regarding diagnostic studies from neuroimaging to Gram stains. A special chapter on techniques for examining pediatric patients is quite helpful. The remainder of the text is divided into traumatic and nontraumatic ocular emergencies. Both sections are well written, and the chapters on sudden visual loss and functional disorders are particularly good. The book finishes with two chapters dealing solely with ophthalmic infections and antibiotic and steroid use. An excellent appendix listing all ophthalmologic abbreviations and notations in common use is a godsend to beginning residents and physicians in other specialties.

All beginning ophthalmology and emergency medicine residents, to whom this text is directed, would benefit from reading this book. Its easy-to-read text and almost 300 clear illustrations leave one with a solid basic understanding of most entities he is likely to encounter in the emergency setting. Others in practice or those preparing for board examinations would find it an excellent review book as well. Priced moderately, Ocular Emergencies is a welcome addition to the ophthalmologic literature.

R. M. Siatkowski, M.D.
Fellow, Pediatric Ophthalmology
Bascom Palmer Eye Institute
Miami, Florida


Written for general ophthalmologists and ophthalmologists-in-training, this book gives a basic overview into a very common disease. After beginning with its epidemiology, Marilyn Kincaid and Alan Bird review the pathology and pathophysiology of AMD. Drs. Hampton and Nelsen then discuss the office evaluation and mechanics of fluorescein angiography. Following is an excellent chapter by Mary Lou Lewis on the clinical presentations of AMD. The authors then review basic concepts of and indications for laser therapy. Two well-written chapters examine the current status of medical and surgical management of this entity. The final section reviews the low vision evaluation and various resources for patients with AMD, and concludes with an essay from the patient's perspective. Age Related Macular Degeneration accomplishes its goals of describing the various features of this disease, how to evaluate the patient, when to order fluorescein angiography, and when to treat or refer.

R. M. Siatkowski, M.D.
Fellow, Pediatric Ophthalmology
Bascom Palmer Eye Institute
Miami, Florida

Two patients with angioedema of the eyelids and orbits are described in whom skin biopsy disclosed a necrotizing vasculitis. This condition is discussed with highlighting of ophthalmic manifestations.

*Lyn A. Sedwick, M.D.*


Four patients with ocular ischemic syndrome (hypotony, uveitis, corneal edema, and visual loss resulting from decreased ocular perfusion) were found to have biopsy-proven giant cell arteritis. Three patients had jaw claudication, one of these had headaches, and one patient had only ocular pain. Another unusual but important presentation of this disease.

*Lyn A. Sedwick, M.D.*


An infant with Joubert's syndrome also was found to have probable ocular fibrosis and histidineemia. The authors believe these two diagnoses may be related and recommend histidine assays on patients with Joubert's or ocular fibrosis.

*Lyn A. Sedwick, M.D.*

Long-Term Results of Adjustable Suture Surgery for Strabismus Secondary to Thyroid Ophthalmopathy. Lueder GT, Scott WE, Kutschke PJ, Keech RV. *Ophthalmology* 1992;99:987-92 (June). [Reprint requests to Dr. W. E. Scott, University of Iowa Hospitals and Clinics, Department of Ophthalmology, Iowa City, IA 52242.]

Records of 1524 patients with thyroid ophthalmopathy were reviewed and 47 identified who had adjustable suture surgery with average follow-up of 41 months. Results were good or excellent in 73%, fair in 19%, and poor in 9%. Complications of the surgery are discussed as is the use of prisms. The authors feel adjustable sutures are an effective surgical therapy in selected patients with thyroid ophthalmopathy.

*Lyn A. Sedwick, M.D.*

Intraocular and Central Nervous System Lymphoma in a Cardiac Transplant Recipient. Johnson BL. *Ophthalmology* 1992;99:987-92 (June). [Reprint requests to Dr. B. L. Johnson, Eye Pathology Laboratory, Eye and Ear Institute, 203 Lothrop St., Pittsburgh, PA 15213.]

A 69-year-old lady on cyclosporine and azathioprine following heart transplant 2 years previously developed vitreous cells and retinal infiltrates thought to be secondary to toxoplasmosis. She responded only partly to appropriate therapy for toxoplasmosis and ultimately had increased vitreous cells, decreased ocular motility, and an orbital mass with cranial extension on magnetic resonance scan, biopsy of which showed large-cell malignant lymphoma (reticulum cell sarcoma). Autopsy
5 weeks later showed no systemic involvement. This entity is discussed.

Lyn A. Sedwick, M.D.

**Paroxysmal Eyelid Retractions.** Lam BL, Nerad JA, Thompson HS. *Am J Ophthalmol* 1992;114:105-7 (July). [Inquiries to Dr. J. A. Nerad, Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.]

A 3-year-old boy with bilateral traumatic third nerve palsies subsequently developed isolated episodic upper eyelid retractions approximately 2 years later which resolved in 2 months. No other muscles innervated by the third nerve were involved and the authors contrast this previously unreported phenomenon to ocular neuromyotonia and oculomotor paresis with cyclic spasms.

Lyn A. Sedwick, M.D.

**Superior Rectus Overaction After Cataract Extraction.** Grimmett MR, Lambert SR. *Am J Ophthalmol* 1992;114:72-80 (July). [Reprint requests to Dr. S R. Lambert, Emory Eye Center, Room 5826, 1327 Clifton Rd. N.E., Atlanta, GA 30322.]

Four cases of patients with post-cataract surgery ipsilateral overaction of the superior rectus muscle were studied. Other causes of strabismus were diligently excluded, and the authors concluded that these cases resulted from a temporary paralysis or weakening of the antagonist muscle, i.e., inferior rectus, sustained from the retrobulbar anesthetic, which led to overaction of the superior rectus.

Lyn A. Sedwick, M.D.


A 47-year-old man had a subdural hematoma in the posterior fossa, which was drained. Eight months later he demonstrated Parinaud’s syndrome only with his head flexed. Computed tomographic scanning showed a subdural fluid pocket over the left cerebellar hemisphere and distortion of the collicular plate from shift of the cerebellum. The authors believe these CT findings resulted in intermittent compromise of cerebrospinal fluid flow through the third ventricle and compression of the posterior commissure.

Lyn A. Sedwick, M.D.

**Diagnosis of Cavernous Sinus Arteriovenous Fistula by Measurement of Ocular Pulse Amplitude.** Golnik KC, Miller NR. *Ophthalmology* 1992;99:1146-52 (July). [Correspondence to Dr. K. C. Golnik, Department of Ophthalmology, Medical College of South Carolina, 171 Ashley Ave, Charleston, SC 29425-2236.]

The authors used ocular pulse amplitude measurement from pneumotonometry readings to show a significant difference in patients with carotid cavernous fistulas. These patients were compared to other patients with orbital and neurologic disease. In all cases ocular pulse amplitudes were elevated only in patients with carotid cavernous fistulas. The authors feel this is a “sensitive, specific, safe, and simple method of identifying patients with both direct and dural cavernous sinus arteriovenous fistulas.”

Lyn A. Sedwick, M.D.


A 58-year-old man with sudden complete loss of vision left eye with near total recovery over 2 days is presented. A refractile body was seen in an inferior retinal arteriole. The discussants present their ideas regarding current management of such a patient and briefly review the results of the North American Symptomatic Carotid Endarterectomy Trial.

The authors report three cases of presumed chiasmal glioma (all with magnetic resonance imaging) followed for considerable periods of time (8½ years, 4 years, 5 years) who demonstrated modest to considerable improvement in visual function without any surgical or radiation therapy intervention. Other similar reported cases are discussed as well as possible mechanisms.

Lyn A. Sedwick, M.D.


A 6-year-old with episodic jerk nystagmus is presented. He had excision of a posterior fossa ependymoma 2 years previously followed by chemotherapy and radiation treatment. Magnetic resonance showed no tumor recurrence. Baclofen treatment markedly reduced the number, duration, and intensity of episodes.

Lyn A. Sedwick, M.D.


The authors report on photopsia and formed hallucinations experienced by 67 of 100 consecutive patients with macular choroidal neovascularization from macular degeneration. In most of these patients, visual acuity was very poor in each eye. The discussion section, particularly in regard to hallucinations, is excellent.

Lyn A. Sedwick, M.D.


A 30-year-old man presented with bilateral progressive exophthalmos. Computed tomographic scanning demonstrated large heterogeneous masses superiorly in both orbits, which were surgically removed and found to be neurofibromata. The patient's general physical findings were suggestive of multiple endocrine neoplasia type IIb, which was felt to be the cause of his neurofibromata.

Lyn A. Sedwick, M.D.


Magnetic resonance imaging was used in 12 patients with orbital lymphangioma and provided "optimal imaging" of these tumors mainly because of its ability to distinguish acute and chronic hemorrhage. It was also useful for identifying large-tumor feeding vessels. Excellent magnetic resonance images are provided in this article.

Lyn A. Sedwick, M.D.


A case of leukemic infiltration of the optic nerve is presented with color disc photographs and confirmatory axial and coronal magnetic resonance images. As the authors note, computed tomography has been a "rather insensitive method for detecting abnormalities in patients with leukemic infiltration of the optic nerve."

Lyn A. Sedwick, M.D.

The authors report two patients with progressive anterior ischemic optic neuropathy who did not undergo optic nerve sheath decompression and over follow-up had quite good return of central acuity, although visual field defects persisted. As they note, we may not know the natural history of this disease process as well as we think we do in order to evaluate the efficacy of optic nerve sheath decompression in its management.

Lyn A. Sedwick, M.D.


The authors present their adaption of "microcryoplaning and computer reconstruction ... in viewing the detailed anatomy of the orbital apex." The microplaning was done with autopsy sections on four heads and compared to computed tomography pictures. They hope their work will ultimately supply information about many normal variants to orbital anatomy, in part to aid in surgery of this region.

Lyn A. Sedwick, M.D.


The authors used this interesting technique to study 21 patients with ocular ischemic syndrome. All patients had high-grade carotid stenosis. Color Doppler demonstrated reduced central retinal artery peak systolic blood flow velocity and reversal of ophthalmic artery flow in 12 of 16 eyes with ocular ischemic syndrome. They also found posterior ciliary artery peak systolic flow velocity to significantly correlate with visual acuity.

Lyn A. Sedwick, M.D.


An interesting volley of letter to the editor and reply from the authors regarding a recently reported case of Lyme disease and retinal artery occlusion. Dr. Winterkorn believes that the patient reported probably had syphilis and that the retinal artery occlusion was incidental. Drs. Lightman, Brod, and Gordon believe that the lab evidence supports Lyme disease and clinical suspicion is high that the retinal artery occlusion was related, given the other ophthalmic findings.

Lyn A. Sedwick, M.D.
To the Editor:

Our vision is interrupted several times a second by saccades, during which the visual world sweeps across the retina. It is a remarkable fact that the smeared image of the visual scene generated by saccadic eye movements is not perceived. There may be several processes contributing to this phenomenon. Holt (1) was the first to propose a "central anaesthesia" initiated by eye movements to account for this lack of vision during saccades. However, Volkmann (2) and Volkmann et al. (3) found that the elevation of visual threshold, and the decrease in contrast sensitivity occurring during saccadic eye movements was small, and unlikely to account for the lack of perception of saccadic blur. More important than such saccadic suppression may be an omission of the perception of the smeared image during saccades: saccadic omission. Psychophysical experiments have concentrated on the importance of forward and backward masking effects in saccadic omission. In these experiments a stimulus preceding or following a saccade obscures the smeared image during the eye movement (4).

We would like to report an observation that suggests saccadic omission can also occur in the absence of any interaction between visual stimuli. The fortification spectra experienced by two of the authors during attacks of classical migraine are congruous and homonymous. They are cortical phenomena. When large saccades were made in a dark room the fortification spectra were clearly lost for a brief but appreciable period, to appear again in the same position in the visual field. This was confirmed in four migraine attacks. In these experiments perception of fortification spectra was lost during saccadic eye movements in the absence of any change in visual stimulation. This therefore indicates a form of saccadic omission which is linked to the eye movement itself.

National Hospital for Neurology and Neurosurgery
London WC1N 3BG
United Kingdom

REFERENCES

A 16-year-old girl tried to commit suicide but "only" the intracranial optic nerves were injured. Her parents brought her to me in the hope that something could still be done. I found myself deeply touched and tried to express my feelings in a poem.

I know that the Journal does not have a poetry (!) section, but I thought that perhaps you might find a place for the English translation of this poem, just to show the nonmedical aspect of our medical profession.

In Vain I am a Doctor

In vain I am a doctor
The bullet speeding through her brain
Blasted the light to nothingness
And I
Condemned to be her doctor
Suddenly
Words flee
Again and again
I postponed
The verdict:
Life blindness
For blind love