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Optic Neuropathy: A Rare Paraneoplastic Syndrome

S. Malik, M.D., A. J. Furlan, M.D., P. J. Sweeney, M.D., G. S. Kosmorsky, D.O., and M. Wong, M.D.

A 63-year-old man developed gradually progressive bilateral loss of vision, cerebellar ataxia, and downbeat nystagmus. Visual acuity was 20/400 OD and 20/200 OS, with cecocentral scotomas OU. Fundus examination showed bilateral optic atrophy and a vitreous cellular reaction. MRI of the brain was normal. CSF protein was elevated, with increased IgG levels but no malignant cells. Biopsy of a pulmonary lymph node showed undifferentiated small cell carcinoma. Neoplastic cells were positive for neuron-specific enolase. Serum contained IgG, which reacted with neuronal and glial cytoplasm and processes. IgG reactivity with systemic tissues and the patient's tumor was not different from that observed with control sera. Paraneoplastic optic neuropathy should be considered in patients with unexplained visual loss and malignancy, and our observations suggest a possible immunologic basis for this condition.

Key Words: Malignancy—Visual loss—Anti-central nervous system antibodies—Immunologic basis.

The paraneoplastic syndromes (PNS) comprise a group of diverse conditions that are manifest as the "remote effect" of certain cancers on the nervous system. They have been recognized for at least 25 years (1–4) and represent the nonmetastatic effect of a remote neoplasm (5). These disorders are rare and occur in less than 1% of unselected patients with cancer.

Optic neuropathy is a particularly rare PNS reported in patients with mixed cell bronchial carcinoma (6), anaplastic oat cell carcinoma of the lung (7–10), Hodgkin's disease (11), and lymphoma (12–14). We report a patient with an initially unexplained, bilateral optic neuropathy and a small cell bronchogenic carcinoma in whom anti-central nervous system antibodies were subsequently demonstrated.

CASE HISTORY

A 63-year-old man with a 40-pack per year history of smoking presented with a 2-month history of gradually progressive bilateral loss of vision. Initially involving the left eye, he described it as a shade across the inferior half of the left visual field, slowly progressing over 3 weeks. This was followed, a month later, by sudden onset, blurring of vision in the right eye. Visual acuity continued to deteriorate over the next month and then stabilized bilaterally. Five months later, he noticed a persistent shimmering of vision bilaterally. This was followed by the subacute development of progressive gait ataxia, clumsiness of the hands, and intention tremor in both arms. There was no history of retinal degenerative disease or exposure to toxins. Past medical history included hypertension, gout, and left internal carotid endarterectomy for high-grade stenosis.

The general physical examination was signifi-
cantly only for a harsh, grade 3/4 systolic murmur over the right upper sternal border, consistent with aortic stenosis. Neurologic examination revealed his mental status to be normal. There were no cranial, ocular, or carotid bruits. Both temporal arteries were soft, pulsating, and nontender. On neuro-ophthalmologic examination, he had a distance visual acuity of 20/200 OU and 20/400 OD and J16 OS at near. The pupillary examination revealed light near dissociation presumed to be secondary to poor visual acuity due to his optic neuropathy. He had coarse, downbeat nystagmus, which increased on lateral gaze. Funduscopic examination revealed moderate arteriolar narrowing and marked A-V nicking. There was bilateral optic disk pallor, with a mild vitreous reaction in the right eye. The extracocular movements were normal. Goldmann perimetry showed bilateral centro-central scotomas and generalized constriction of the visual fields (Fig. 1). No altitudinal defects were noted, despite his complaint of a shade in the inferior visual field. The remainder of the cranial nerve examination was normal. Muscle tone, strength, and sensory examinations were normal. Reflexes were hypoactive and symmetrical, with bilateral flexor plantar responses. Truncal ataxia with asymmetric appendicular ataxia, left greater than right, was present along with an intention tremor and impaired rapid alternating movements. His gait was broad-based and ataxic with an inability to tandem walk. The Romberg test was positive.

Follow-up over 3 months revealed the presence of vitreous cells bilaterally with an enlarging blind spot and central scotoma in the right eye, and a crescentic central scotoma in the left eye. There was a further deterioration of gait and a weight loss of 9 kg.

Results of the laboratory investigation, including complete blood cell count with differential, blood chemistry, serum vitamin B₁₂, thyroid function tests, serologic tests for syphilis, and a chest x-ray were unremarkable. Westergren sedimentation rate, rheumatoid factor, antinuclear antigen profile, and cryoglobulins, as well as serum and urine electrophoresis, were within normal limits. Angiotensin-converting enzyme and β₂-microglobulin were also normal. An echocardiogram revealed moderate to severe aortic stenosis with aortic regurgitation. Carotid ultrasound and magnetic resonance imaging (MRI) of the brain were normal. Cerebrospinal fluid (CSF) analysis revealed a normal pressure of 16 cm of water, 2 RBC/mm³ and 15 WBC/mm³, of which 89% were lymphocytes and 9% were monocytes. The protein level was increased to 72 mg/dl, and the glucose level was normal at 61 mg/dl, with a blood glucose level of 99 mg/dl. Cerebrospinal fluid IgG was increased to 18.7 mg/dl (n = 0.6–4.4 mg/dl), as were the IgG synthesis rate and IgG/albumin ratio to 57.29 mg/day (n = 0–3.1 mg/day) and 0.39 (n = 0.07–0.19), respectively. Oligoclonal bands were absent. Three separate samplings were negative for malignant cells or microorganisms. Pattern-reversal visual evoked responses demonstrated a delay in conduction along both visual pathways. The patient refused to have an electoretinogram.

A bone scan, bone marrow biopsy, and an upper gastrointestinal endoscopy were all normal. A gallium scan, however, revealed intense focal activity over the right perihilar region and computed tomography of the chest showed extensive adenopathy in the retrocaval and azygos regions. Biopsy of the mass revealed a metastatic undifferentiated small cell carcinoma of the lung. The neoplastic cells were strongly positive for neuron-specific enolase and negative for common leukocyte antigen.

The serum contained an IgG which bound diffusely to neuronal and glial cytoplasm and processes of normal human cortex, cerebellum, and optic nerve, and antibody reactivity occurred to an endpoint dilution of 1:800. The IgG reactivity against other systemic tissues did not differ from control sera. Cerebrospinal fluid was not examined for similar antibody reactivity due to the patient's refusal of another lumbar puncture.

A diagnosis of small cell carcinoma of the lung with paraneoplastic optic neuropathy and subacute cerebellar degeneration was made. Direct invasion of the optic nerves by neoplastic cells, though unlikely, could not be definitely excluded.

Radiation therapy to the mediastinum, followed by systemic chemotherapy was instituted, with remission of the tumor. Upon follow-up at 6 months, no fall in antibody titer was observed, and the neurologic and ophthalmologic status remained unchanged. The patient was admitted to another hospital 14 months later (24 months after the onset of illness), due to a recurrence of his tumor, and died. Unfortunately, the family refused permission for an autopsy.

**DISCUSSION**

Optic neuropathy is one of the rarest forms of paraneoplastic syndromes and has been described in only a few case reports (6–14). It is not commonly considered in the differential diagnosis of visual loss, as symptoms may precede the devel-
FIG. 1. A and B: Goldmann visual fields showing the presence of bilateral cecocentral scotomas.

Development of symptoms from the primary neoplasm by many months. In most cases there is bilateral involvement, although it may begin unilaterally. The course is usually one of progressive visual deterioration over several days to weeks (6-8, 10), although loss of vision progressing over a few hours (14), or over a year have also been described (25). In some patients, partial or complete recovery of vision may occur, either spontaneously (8), or after treatment with steroids (10, 13, 14).

The clinical picture initially suggested an anterior ischemic optic neuropathy (AION). The patient complained of loss of vision in the left eye, describing it as a shade over the inferior half of the visual field. This type of visual field loss is characteristically seen in ischemic optic nerve disease.
However, the slow progression of symptoms over 3 weeks, and the absence of an inferior altitudinal defect on Goldmann perimetry are atypical for AION. Although an abrupt onset of visual symptoms, as described by the patient in the right eye, is more common in AION, loss of vision over hours may also be seen in paraneoplastic optic nerve disease (14). Furthermore, the presence of cells in the vitreous are not a feature of AION and pointed more toward an optic neuropathy of either inflammatory or infiltrative origin.

An extensive evaluation for an infectious etiology, connective tissue disorders, vasculitis, and sarcoidosis was negative. The age of the patient and progressive deterioration in his neurological condition, associated with a normal magnetic resonance imaging of the brain and absence of oligodendroclonal bands in the cerebrospinal fluid, made multiple sclerosis an unlikely etiology.

Although meningeal carcinomatosis is common in the setting of a cancer and is often difficult to diagnose in the early stages, the absence of headache, meningeal signs, and multiple cranial nerve palsies suggested a different disorder. The CSF analysis, in addition, on three separate samplings, revealed normal glucose levels and no tumor cells.

The development of a progressive optic neuropathy and prominent cerebellar dysfunction with nystagmus, intention tremor, and ataxia, associated with a small cell carcinoma of the lung in our patient was most consistent with a paraneoplastic syndrome. Subacute cerebellar degeneration is one of the best clinically and pathologically defined paraneoplastic syndromes, and is most often seen with neoplasms of the lung, ovaries, or breast (5). It frequently precedes detection of the tumor and may occur alone or as a part of a wider encephalomyelitis. It is characterized by the progressive development of truncal and appendicular ataxia, nystagmus, and occasionally vertigo.

The pathogenesis of paraneoplastic optic neuropathy is unknown. Various etiologies have been suggested, including (a) microscopic infiltration of the optic nerve by tumor cells (16), (b) an inflammatory response (6), (c) elaboration of a humoral toxin (8,15), or (d) impairment of axonal flow (17). Yet another explanation may be the production of a toxin, inflammatory response (6), elaboration of a humoral response against tumor antigens that are shared by normal neuronal and astrocytic antigens, or by the destruction of neuronal and astrocytic cells containing these antigens. Evidence in support of the former hypothesis has been demonstrated in small cell carcinoma of the lung associated with retinal degeneration (19,24,25).

The neoplastic cells in our patient were strongly positive for neuron-specific enolase, an isoenzyme specific to neurons and amine precursor uptake and decarboxylation (APUD) cells including neuroendocrine cells of the lung (26,27). It is also found in astrocytes as well as in oat cell carcinoma of the lung (28). This protein has been postulated to have an antigenic role in paraneoplastic retinal degeneration associated with oat cell carcinoma of the lung, and may elicit the formation of autoantibodies (18). It is possible that the IgG in the serum of our patient was reactive against neuron-specific enolase. This would explain the diffuse immunoreactivity exhibited against neuronal and astrocytic components of cortex, cerebellum, and optic nerve.

The etiologic significance of the antibody demonstrated in our patient is still uncertain. It may have a role in the development of the visual loss, or may simply be present in the patient’s serum as an epiphenomenon. If a causal relationship can be established, detection of this antibody in patients with unexplained visual loss may be helpful in the early diagnosis of paraneoplastic optic neuropathy and small cell carcinoma of the lung. Subsequent efforts directed at prevention or treatment by immunomodulation may lead to a better systemic and neurologic prognosis.

Acknowledgment: We wish to thank Dr. Kurt Jaeckle in whose laboratory the immunologic testing was done.
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Visual Improvement After Transethmoid-Sphenoid Decompression in Optic Nerve Injuries

Brigitte Ch. Girard, M.D., Evrydiki A. Bouzas, M.D., Georges Lamas, M.D., and Jean Soudant, M.D.

Optic nerve injury as a consequence of blunt head trauma can be responsible for severe and permanent loss of vision. The injury can be direct or indirect and many factors interfere in the development of traumatic optic neuropathy. The exact physiopathological mechanisms remain uncertain.

The management of traumatic optic neuropathy is controversial, especially in cases with total and long-standing loss of vision. Spontaneous visual improvement has been noted, but it is considered to be rare. On the other hand, the efficacy of systemic corticosteroids is still under evaluation. Positive results reported after transethmoid-sphenoid decompression are encouraging. The rarity and severity of traumatic optic neuropathy makes the performance of a controlled treatment study difficult.

We present the results of surgical decompression in a series of 11 patients with traumatic optic nerve neuropathy, in order to contribute to the definition of the indications and the establishment of the usefulness of this surgical procedure.

MATERIALS AND METHODS

Eleven patients with optic neuropathy, which occurred after blunt head injury, were referred to the department of otorhinolaryngology of the Pitie-Salpetriere Hospital (Paris, France). There were 9 men and 2 women, 12 to 61 years of age (average 32 years) (Table 1). The cause and violence of the injury was variable; 6 of 11 patients had loss of consciousness.

The diagnosis of indirect optic nerve trauma was based on loss of vision, lack of direct pupillary light reflex, and intact consensual response. Par-
TABLE 1. Characteristics and visual acuities of patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Delay (days)</th>
<th>Initial visual acuity</th>
<th>Final visual acuity</th>
<th>Follow-up (months)</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>26</td>
<td>1</td>
<td>20/100</td>
<td></td>
<td>2</td>
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<td>3</td>
<td>M</td>
<td>61</td>
<td>5</td>
<td>CF 3 m</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>19</td>
<td>7</td>
<td>0</td>
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<td>6</td>
<td>F</td>
<td>19</td>
<td>15</td>
<td>CF 1 m</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>M</td>
<td>18</td>
<td>17</td>
<td>20/40</td>
<td>20/30</td>
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<tr>
<td>8</td>
<td>M</td>
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<td>9</td>
<td>M</td>
<td>42</td>
<td>43</td>
<td>HM</td>
<td>CF 1 m</td>
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</tr>
<tr>
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<td>M</td>
<td>57</td>
<td>46</td>
<td>HM</td>
<td>20/200</td>
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<tr>
<td>11</td>
<td>M</td>
<td>42</td>
<td>92</td>
<td>LP</td>
<td>20/70</td>
<td>18</td>
</tr>
</tbody>
</table>

M, male; F, female; CF, count fingers; m, meters; HM, perception of hand motion at 0.2 m; LP, light perception.

ticular attention was paid to the latter sign in order to exclude anatomic optic nerve section. Complete interruption of the nerve conduction leads to total pupillary akinesia. Patients with eyeball trauma or other ocular lesions were excluded. All patients underwent a complete neuro-ophthalmic examination before surgery in order to evaluate the initial lesion. Visual acuity measurements are reported in Table 1. Goldmann visual fields were performed, vision permitting. Radiography and computed tomography scan focused on the optic canal contributed to the initial evaluation.

The interval between injury and surgery depended on the patient's general health and the delay in consulting an ophthalmologist. This varied from 24 hours to 92 days, with an average of 25 days. Of the 11 patients, 7 were operated on before the end of the third posttraumatic week. The same surgical technique of transethmoidal-sphenoidal decompression of the optic nerve was used for all patients, as described (1,2). Surgery was performed under general anesthesia, with the use of the operating microscope. Follow-up neuro-ophthalmological examinations were done 1 day, 1 week, 1, 2, 3, and 6 months after the operation, and then every 6 months whenever possible (Table 1).

RESULTS

No intraoperative complications were noticed. The only postoperative complication observed was a transient abducens paralysis (patient 7), which left no oculomotor sequela.

Visual recovery of these 11 patients was variable. Evolution of visual acuities and visual fields are summarized in Table 1 and Figs. 1 and 2. Excellent results were noticed in one case (patient 8) whose visual acuity improved from "no light perception" to 20/25, despite 5 weeks interval between trauma and surgery. During the operation a bone fragment was found close to the optic nerve and was removed. Good results were noted in five patients (1, 7, 8, 10, and 11). They showed expansion of their visual fields and recovery of a numbered visual acuity. Moderate improvement was noted in three patients (3, 6, and 9), whose vision increased from total blindness without light perception or hand movement perception to "counting fingers," accompanied by an improvement in visual fields. No functional improvement was noticed in three cases (patients 2, 4, and 5). In this group, severe lesions were found during the operation: multiple fractures of the optic canal associated with fractures of other bones.

In most of the patients responding to the treatment the improvement of the visual function was obvious on the first postoperative day. However, an additional delayed improvement was not unusual during the first months of the follow-up period.

DISCUSSION

Indirect optic nerve injury is a severe consequence of blunt head trauma, often resulting in blindness (3-6). The optic nerve is very sensitive to ischemia and compression in the optic canal. Edema secondary to ischemia increases mechanical compression (7-9). The demonstration of nerve infarction in the intracanalicular portion of the nerve on pathology specimens supports the theory of vascular participation in the pathophysiology of traumatic neuropathy (7,8). Those observations provide theoretical support to the surgical decompression of the optic nerve in the canal after indirect optic nerve injury.

Spontaneous visual improvement has been reported either anecdotally (10,11) either in small series of patients with a frequency of 20-38% (12-14). Hughes reported 9 cases of recovery in a series of 56 consecutive patients with traumatic optic neuropathy (3). Different therapeutic approaches have been proposed in order to increase the chances of functional recovery. Medical treatment consists in intravenous high-dose or megadose of corticosteroids and led to the improvement of visual function in 45-70% of the patients in different reports (12,14-21). Surgical treatment became more popular after the development of extracranial ap-

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approaches of optic nerve decompression, as by Niho et al. (22) and Fukado (23). These techniques replaced the more morbid and less efficient neurosurgical route (3,24,25).

In our study, 11 patients with traumatic optic neuropathy underwent surgical decompression by transthemoid-sphenoid route; 8 patients showed visual recovery based on visual acuity and visual field testing. Good results of extracranial optic nerve decompression after indirect injury have previously been reported by several authors (1,13,15,18,22,23,26–28). Recently visual improvement has been reported by Joseph et al. (2) in 11 of 14 patients with traumatic optic neuropathy after transthemoid-sphenoid decompression.

None of the above-mentioned studies is controlled. However, the comparison of the results presented herein and previously reported in the literature with reports of spontaneous recovery show better results after optic nerve decompression. A double-blind study evaluating efficacy of medical treatment and surgical decompression has never been performed. Comparison of different series reporting results of medical and surgical treatment reveal better results after surgical decompression, but the fact that some of the patients operated on in these series had also had corticotherapy makes the interpretation of the results difficult. However, surgical decompression is reported to be rapidly successful even in patients...
who fail to respond to steroid therapy (12,18,20, 21,28). In our series none of the patients had corticotherapy before or after surgery. The results reported can thus be attributed to the effect of the surgical treatment. Spontaneous recovery seems improbable but cannot be excluded, although most of the functional recovery became manifest soon after the operation.

Most of our patients have been operated on during the first 3 weeks after trauma. However in Cases 8–11, delayed surgical decompression up to 92 days after the trauma did not exclude the possibility of improvement in visual function. Positive results after delayed surgery have rarely been reported (18,23), but surgery performed later than 7 days after the injury is considered to be nonefficient by other authors (2,20).

Permanent loss of vision had been considered a contraindication for any therapeutic attempt (4,15, 20,25,27). However, 4 of 7 of our patients presenting with total blindness regained some visual function after surgical decompression, as in some cases previously reported (2,11,18).

As it has frequently been mentioned (2,14,25,29) a large, randomized, prospective, multicentric study would be useful for the evaluation of the management of traumatic optic neuropathy, but its rarity and severity make this very difficult. The results reported by our series are in favor of the transethmoid-sphenoid decompression, which ap-
FIG. 2. Visual fields before (A) and after (B) optic nerve decompression (OND) of patient 9. Visual field's before (C) and after OND (D) of patient 10. Visual field before (E) and after OND (F) of patient 11.
FIG. 2. Continued.
peared safe and efficient even in cases with total blindness and, sometimes, despite a delayed treatment. However, as there is no proof that the recovery is directly related to the interval between trauma and surgery, a trial period of corticotherapy might be suggested.

**REFERENCES**

Sixth Nerve Palsy as the Initial Presenting Sign of Metastatic Prostate Cancer
A Case Report and Review of the Literature

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Cranial nerve palsies secondary to metastatic prostate cancer are uncommon occurrences. Usually appearing late in the course of the disease, they are associated with a poor prognosis. We report a case of a 71-year-old man who initially complained of diplopia and was found to have a right sixth nerve palsy and hyperdeviation caused by a mass in the clivus. Biopsy of the mass and extensive systemic workup revealed metastatic adenocarcinoma of the prostate gland.

Key Words: Sixth nerve palsy—Hyperdeviation—Metastatic prostate carcinoma—Clivus—Initial presentation.

The causes of abducens nerve deficits are numerous. Other than isolated sixth nerve palsies causing lateral rectus dysfunction, pathologic conditions that must be considered in the differential diagnosis include Graves' orbitopathy, myositis, myasthenia gravis, orbital trauma, congenital defects (e.g., Duane's retraction syndrome or Möbius syndrome) and convergence spasm (1). These neuro-ophthalmologic entities are nearly always associated with other symptoms or physical findings. The differential diagnosis of isolated sixth nerve deficits is equally extensive. Nonlocalizing processes include increased intracranial pressure, head trauma, postlumbar puncture, vascular hypertension, diabetes mellitus, parainfectious syndromes (postviral or otitis media in children), or basilar meningitis (1). Localizing mass lesions include pontine syndromes, cerebellopontine angle lesions, clivus lesions, middle fossa disorders, and cavernous sinus or dural arteriovenous fistula (1). Again, most of these conditions are associated with additional findings other than the lateral rectus paresis.

CASE SUMMARY

A 71-year-old man presented to an Australian general practitioner with complaints of sudden onset of diplopia. Images were displaced horizontally and vertically. There were no associated headaches, nausea, or vomiting. The patient also denied photophobia, eye pain, and decreasing central or peripheral vision. Past medical history was remarkable for a myocardial infarction in 1982. Benign prostatic hypertrophy was described on past
physical examinations. His medications included acetaminophen, antacids, stool softeners, and flurazepam. Review of systems was significant for an occasional nonproductive cough and blood occasionally seen on toilet tissue after a bowel movement. Upon specific questioning, he did admit to chronic decreased force of urinary stream. Prior to the onset of diplopia, the patient had seen another general practitioner for low back pain that radiated down his left leg. He was injected with an unknown medication, and the pain resolved within 6 days. A computed tomography (CT) scan was performed in Australia, which reportedly revealed a pituitary tumor. The patient was referred to Fitzsimons Army Medical Center for further evaluation.

Ocular examination was requested to evaluate his complaints of diplopia. Visual acuity was 20/20 OU. Pupils were equal, round, and briskly reactive OU without a relative afferent pupillary defect. Slit lamp examination was normal. Motility examination revealed decreased abduction OD. A incomitant esotropia of 10 prism diopters in primary position was seen, which increased to 18 prism diopters in right gaze. A constant 2 to 4 PD right hypertropia was present in all fields of gaze. Automated visual field testing was entirely normal. Dilated fundus examination was essentially normal except for scattered drusen in the macula and myelinated nerve fibers along the inferotemporal arcade OD. A flame-shaped hemorrhage was seen along the superonasal arcade OS. Physical examination other than the ocular examination was normal except for diffuse enlargement of the prostate gland. No nodules were appreciated. Neurologic examination was intact except for presence of the ocular motility disturbance.

The patient was admitted to the neurosurgical service with the diagnosis of a primary pituitary tumor. The Endocrinology Service performed an extensive workup, which included hormone assay studies. Screening serum chemistries and blood count were remarkable for hematocrit of 38.2 ml/100 ml and a Wintrobe sedimentation rate of 35 mm/h. In order to better define the lesion seen on CT scan, magnetic resonance imaging (MRI) of the head was obtained. This revealed an expansile, low-to-moderate signal intensity lesion, causing bony erosion of the clivus, which was enhanced with gadolinium (Figs. 1 and 2). The lesion was compressing the sella superiorly and extending into the sphenoid sinus. This tumor was felt to be most consistent with a chordoma, rather than a pituitary adenoma. At this time, the endocrine assays returned and were within normal limits. Lumbosacral spine radiographs were then obtained to evaluate the patient’s recurring back pain. These revealed possible metastatic disease in the spine. A bone scan was then obtained, which showed multiple metastatic foci in the ribs, thoracic spine, sternum, pelvis, and right femoral shaft. MRI of the lumbosacral spine confirmed the metastatic appearance of the lesions on the radiographs. Gastroenterologic evaluations, which included colonoscopy and air-contrast barium enema failed to yield the site of the primary tumor. The patient was then seen by the Urology Service
for the evaluation of his enlarged prostate gland. Prostatic acid phosphatase and prostatic specific antigen levels were drawn and returned elevated. A needle biopsy of the prostate gland showed adenocarcinoma of the prostate gland, Gaeta grade III classification (Fig. 3). A bilateral orchietomy was performed for androgen ablation therapy. After his recovery, the patient was returned to the operating room where he underwent transsphenoidal subtotal resection of the clivus tumor. Frozen section histopathologic analysis at the time of resection revealed "bone fragments with osteoblastic reaction and tumor cells with microacini cannot rule out metastatic tumor." Permanent section confirmed the diagnosis of metastatic adenocarcinoma (Fig. 4). The patient was then referred to Radiation Oncology for parasellar region radiotherapy of the metastasis.

**DISCUSSION**

This is the first reported case of unrecognized adenocarcinoma of the prostate gland metastatic to the clivus initially presenting as a lateral rectus palsy associated with a hyperdeviation. Isolated sixth nerve palsies are commonly due to ischemic mononeuropathy, for example, diabetes or hypertension (1). Vascular inflammation, such as cranial arteritis, would be unusual, but must be considered in an elderly patient (1). Aneurysmal dilatation of the posterior inferior cerebellar artery or basilar artery has also been reported to cause abducens deficits usually associated with severe headaches (1).

Tumors may compress the sixth cranial nerve as it ascends vertically through the subarachnoid space to enter the dura overlying the clivus. Primary tumors include chordoma and other rare tumors of the bones of the skull: osteomas, chondromas, osteochondromas, osteoclastomas, aneurysmal bone cysts, or intrasosseous hemangiomas (1). Nasopharyngeal carcinoma may extend superiorly into the cavernous sinus to infiltrate or compress the abducens nerve often damaging other structures in the cavernous sinus. It can also cause ipsilateral postganglionic Horner's syndrome, since the oculosympathetic pathways join briefly with the sixth cranial nerve in the cavernous sinus (1). Metastatic lesions, most often carcinomas, can spread to the central nervous system, usually via hematogenous dissemination. Lung and breast carcinomas are most common; however, other metastatic tumors include kidney, stomach, prostate, and thyroid (2). The frequency of metastatic spread is most closely related to the relative incidence of the tumors themselves.

Cranial nerve dysfunction secondary to metastatic prostate carcinoma has been reported previously in 34 patients (3-6). These rare cranial nerve deficits are due to the expansive nature of the bony metastases at the base of the skull, which either compress or infiltrate the affected nerves. In most

![FIG. 3. Micrograph of prostate gland biopsy showing poorly differentiated adenocarcinoma. (Hematoxylin and eosin; original magnification ×100.)](image-url)
instances, multiple cranial nerves are involved and occur late in the course of the disease process. In all but two of the cases, prostate adenocarcinoma was diagnosed months to years prior to the onset of cranial nerve palsies. Of the cases that initially presented with cranial nerve dysfunction, one patient who complained of right ear pain and headache had imaging studies that showed a lesion involving cranial nerve XII (3). In the second case, a patient complained of diplopia and exophthalmos, with a lesion involving the 3rd and 6th cranial nerves (3). On CT scan, a mass was seen destroying bone in the region of the orbit. Sixth nerve palsies occurred in isolation in only 4 of the 34 patients reported in the literature (3-5).

Metastatic spread of adenocarcinoma of the prostate gland is extremely common. At autopsy, the bones most frequently involved, in descending
order, are the spine, femur, pelvis, ribs, sternum, skull, and humerus (1,7,8). When the skull becomes involved, metastatic foci are prominent in other bones. Skull metastases, when present, are usually found in the calvaria (9). Erosion of the clivus is an exceedingly uncommon event. In a review of the literature of metastatic prostate carcinoma to the skull, only three cases are described as having clivus metastases (3). Of these, none had a metastatic clivus lesion as their initial presentation. However, in one patient, the clivus metastasis occurred 14 years after prostate cancer was initially diagnosed, presenting with multiple neurologic manifestations.

Hyperdeviations have been described previously in association with isolated unilateral abducens palsies (10–12). Slavin (11) found hyperdeviations in a series of 16 patients. The amount of deviation ranged from 4 to 16 prism diopters. In 10 of the cases, the associated hyperdeviation was found in primary gaze as well as peripheral fields of gaze. It was also noted that there was no correlation between degree of abducens deficit and magnitude of the hyperdeviation. In only two of the cases could Slavin (11) explain the hyperdeviation in pathologic terms. In one patient with multiple sclerosis, the deviation may have been due to a supranuclear disturbance, that is, skew deviation. In the second case, the subtle hyperdeviation was thought to be due to a right superior oblique palsy. Baker and Buncic (12) describe three cases of pseudotumor cerebri in which there was an abducens palsy associated with vertical deviation. In all the cases, the hyperdeviation resolved after intracranial pressure was normalized.

Even though this appears to be an isolated case, metastasis to the clivus by prostate carcinoma must be included in the differential diagnosis of 6th nerve palsies in males.

REFERENCES
Chronic Idiopathic Inflammation of the Retropharyngeal Space Presenting with Sequential Abducens Palsies

Maher M. Fanous, M.D., Curtis E. Margo, M.D., and Latif M. Hamed, M.D.

We describe a patient who presented with sequential, bilateral abducens palsies associated with a mass of the nasopharynx. Biopsy of the mass showed chronic non-specific inflammation and fibrosis. The diagnosis of idiopathic inflammatory pseudotumor was arrived at by exclusion of other known causes of inflammation of the retropharyngeal space. Magnetic resonance imaging suggested that injury to the sixth cranial nerves probably occurred as they traversed the dura and subarachnoid space overlying the clivus.

Key Words: Idiopathic inflammatory pseudotumor—Sequential abducens palsies.

The loose connective tissue that exists between the middle and deep layers of the deep cervical fascia resides within the retropharyngeal space. Superiorly the fascia is bound by the sphenoid bone and clivus, and is contiguous on each side to the carotid sheath. Caudally, the retropharyngeal space is continuous with the mediastium (1). Primary disease processes within this space are rare (1,2). We describe a patient with an idiopathic inflammatory pseudotumor of the retronasopharyngeal space, who presented with sequential sixth nerve palsies.

REPORT OF A CASE

A 39-year-old man presented to the eye clinic with a 1-month history of horizontal diplopia and intermittent frontal headaches. He had a history of multiple substance abuse, including intravenous and intranasal cocaine but was otherwise healthy. Clinical evaluation showed an isolated partial right sixth nerve palsy with otherwise normal ocular and physical examinations. A computed tomogram showed thickening of the mucosal lining of the sphenoid sinus. Magnetic resonance (MR) revealed abnormal signals arising from the mucosa and periosteum of the sphenoid sinus and from the dura overlying the clivus. Laboratory studies including serologic tests for syphilis (rapid plasma reagin and hemagglutination treponemal test for syphilis (HATTS)), antinuclear antibodies, anticyttoplasmic neutrophilic antibodies, and angiotensin-converting enzyme were all normal. Sickle cell preparation and Lyme titer were negative. IgM antibody to Epstein-Barr viral capsid antigen was negative. Chest x-ray was normal, but a purified protein derivative of tuberculin skin test was positive (unknown conversion time). Serum human
immunodeficiency virus (HIV) antibody assay was negative. The patient refused lumbar puncture and was treated empirically with INH (isoniazid) and pyridoxine.

Two months later, the ocular dysmotility progressed. Examination revealed isolated bilateral sixth nerve palsy (Fig. 1). General and neurologic examinations were normal. Laboratory tests were again normal, including negative serologic tests for syphilis and HIV. Ocular forced ductions and a Tensilon test were negative. Lumbar puncture revealed a normal opening pressure and normal chemical profile of the cerebral spinal fluid; the cerebrospinal fluid contained 24 WBC/dl with 88% lymphocytes, 5% monocytes, 7% neutrophils, and no erythrocytes. The cryptococcal antigen titer was negative; bacterial and fungal cultures showed no growth.

A repeat MR showed a mass lesion of the retropharyngeal space at the level of the nasopharynx (Fig. 2). There was persistent mucoperiosteal thickening of the sphenoid sinus and further meningeal enhancement overlying the clivus. Nasopharyngeal biopsies revealed nonspecific chronic inflammation with focal lymphoid hyperplasia and fibrosis (Fig. 3). There was no evidence of vasculitis, necrosis, or granuloma formation. Immunoperoxidase stains for immunoglobulins showed a polyclonal population of lymphocytes. Bacterial and fungal cultures of the biopsy tissue were negative.

The bilateral abducens palsy remained stable over a 17-month follow-up. MR scans 6 and 13 months after the onset of symptoms revealed the same findings as detailed above. Additional biopsies from the nasopharynx were obtained on two separate occasions during the 17-month interval of follow-up; both showed chronic nonspecific inflammation, although the proportion of fibroconnective tissue increased in each successive biopsy. Bacterial and fungal cultures were negative on each occasion.

FIG. 1. The patient is esotropic in primary position and has bilateral limitation of abduction, more severe on the left side.
M. M. FANOUS ET AL.

in repeat biopsy specimens increased, so that sensitivity to corticosteroids would theoretically be less. There also was concern that corticosteroids could potentially aggravate the osteolytic sinusitis in a cocaine user.

Nonspecific inflammation of the retropharyngeal space has been described in patients with AIDS (6). The possibility of AIDS cannot be absolutely excluded in our patient. His history of drug use places him at risk, although two negative serologic tests for HIV and the absence of other signs of immune dysfunction make the diagnosis of AIDS unlikely.

Injury to the sixth cranial nerves in our patient might have occurred as they traversed the dura or subarachnoid space overlying the clivus where they are vulnerable to injury from chronic inflammation. The mild, chronic pleocytosis found in the cerebral spinal fluid is consistent with a parameeningeal focus of inflammation.

FIG. 2. Magnetic resonance with gadolinium, sagittal view, showing enhancement of the dural-venous plexus in the area of the sphenoid sinus and clivus, and a mass lesion in the retropharyngeal space (arrows).

FIG. 3. Biopsy from the nasopharynx showing chronic inflammation. A germinal center (lower right corner) is surrounded by mature lymphocytes. (Hematoxylin-eosin, ×175.)
Intranasal cocaine use has been associated with chronic osteolytic sinusitis, chronic inflammation of the orbit, and optic neuritis (8–10). Cranial neuropathies are probably due to contiguous inflammation. The mechanism by which intranasal cocaine causes these complications is unclear, although the concurrent use of nasal sprays containing steroids and vasoconstrictors may contribute to osteolysis (8). The history of drug abuse in our patient may be coincidental with his inflammatory processes, although the possibility that the two are causally related cannot be completely discounted.

REFERENCES
Papilledema and Intraspinal Lumbar Paraganglioma

David R. Hardten, M.D., Dennis Y. Wen, M.B., B.S., Jonathan D. Wirtschafter, M.D., Joo H. Sung, M.D., and Donald L. Erickson, M.D.

Optic nervehead swelling is most frequently caused by ocular or intracranial lesions. The case presented here demonstrates that the spinal subarachnoid space must also be considered as a potential site for a lesion causing optic nervehead swelling. A 56-year-old man is presented with an intraspinal lumbar paraganglioma associated with increased cerebrospinal fluid protein, papilledema, transient obscurations of vision, and back pain. This may be the first reported case of a paraganglioma associated with optic nervehead swelling. Magnetic resonance imaging of the lumbosacral region revealed the lesion noninvasively. The papilledema, transient obscurations of vision, and back pain resolved after resection of the tumor. The mechanisms are not defined for optic nervehead swelling in association with spinal tumors in general and paraganglioma in particular. The measured abnormal elevation of cerebrospinal fluid protein may have resulted in increased intracranial pressure and papilledema.

Key Words: Optic nerve head swelling—Paraganglioma—Spinal cord lesion—Papilledema—Magnetic resonance imaging (MRI).

CASE HISTORY

The patient was a 56-year-old male who presented with a 1½-year history of intermittent dimming of his vision, which occurred several times each day. He had experienced mild headaches for several years. Back pain had been present for more than 30 years since a minor injury while in military service, but had worsened over the last 6 years. He had noted radicular pain and numbness down his right leg in the last 2 years. He was unable to lie comfortably for more than 2 hours at a time because of the pain.

Past medical history was remarkable for hypertension, atrial fibrillation, and nephrolithiasis. Medications were nicardipine, quinidine, hydrochlorothiazide/triamterene, digoxin, bumetanide, naproxen, and aspirin. In the year prior to referral to our center, optic nervehead swelling was noted, and evaluation included normal brain and lumbar spine computed tomography. Electromyelography revealed bilateral borderline conduction velocities of lumbar motor and sensory nerves, and dener-
vation potentials in the L4-5 distribution on the right suggestive of a radiculopathy. Lumbar puncture performed at the L3-4 level revealed 6,400 RBC/mm³, 200 WBC/mm³, and a protein of 2,022 mg/dl.

Upon referral to our institution, physical examination revealed deep tendon reflexes to be symmetric but reduced in the lower extremities. Motor strength and muscle bulk was normal, and straight leg raising was negative. Visual acuity in the right eye was 20/20, and in the left eye was 20/15. Contrast sensitivity testing with wall-mounted plates (Vistech, Dayton, OH) revealed decreased sensitivity in both eyes at higher spatial frequencies, with the right eye showing poorer responses than the left. Goldmann visual field testing showed bilateral enlargement of the physiologic blind spot. Fundus examination demonstrated bilateral optic nervehead swelling and nerve fiber layer hemorrhages (Fig. 1).

Magnetic resonance imaging of the head revealed multiple nonspecific punctate signal aber-

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**FIG. 1.** (A) Right optic nervehead showing nerve fiber layer hemorrhages and axonal swelling. (B) Left optic nervehead showing nerve fiber layer hemorrhages and axonal swelling.
rations in the white matter (Fig. 2). Because of the association of back pain with the optic nervehead swelling a lumbar spine MRI was performed. Spine MRI revealed an enhancing intradural mass at L1-2 (Fig. 3). The patient underwent lumbar laminectomy and total excision of a well-encapsulated, but rather adherent intradural mass, arising from a lumbar nerve root, which measured 4 x 2 cm. Cerebrospinal fluid (CSF) was removed rostral to the tumor during surgery revealing 0-2 RBC/mm$^3$ and a protein of 182 mg/dl.

The biopsied mass was histologically characteristic for paraganglioma. The tumor was cellular and strikingly lobulated by delicate vascular stroma (Fig. 4). The tumor cells were uniform and epithelioid, having round or oval nuclei, and watery or pale granular cytoplasm in hematoxylin and eosin stain. With immunoperoxidase stain of the paraffin section with antiserum against chromogranin, a majority of the tumor cells exhibited strong reactivity.

Two months postoperatively the visual acuity was 20/15 in each eye, and there was resolution of the transient visual obscurations, headaches, and radicular back pain. The papilledema was markedly improved, and small golden dots were seen in the region of the papillomacular bundle compatible with resolving papilledema.

**DISCUSSION**

Although optic nervehead swelling most commonly occurs in optic neuritis, anterior ischemic optic neuropathy, benign intracranial hypertension, and intracranial mass lesions, spinal neoplasms have occasionally been associated with papilledema (1-14). In this patient an unusual lesion, an intradural lumbar paraganglioma, caused visual symptoms and optic nervehead swelling, which resolved after removal of the lesion. Despite several reports of spinal cord tumors associated with increased intracranial pressure and papilledema, the pathophysiology remains poorly understood. A wide range of mechanisms have been described to account for this phenomenon of increased intracranial pressure and papilledema secondary to a spinal cord tumor. The majority of mechanisms concentrate on the effects of the tumor or tumor products on the normal CSF resorption mechanisms. Paraganglioma is a relatively unusual tumor in the spinal column, with about 80 cases reported in the literature, but it has not been previously associated with optic nervehead swelling (15-17).
Elevated CSF protein in intradural tumors may arise from several sources. Recurrent spontaneous bleeding into the subarachnoid space may occur in ependymomas, which are the predominant tumors associated with this phenomenon (14). Tumor material may also break down, or the tumor may spread throughout the extra and intracranial subarachnoid space, blocking the CSF drainage channels. Such tumor spread is frequent in ependymomas (9). Increased protein may result from active secretion of protein by the tumor or transudation from leaky tumor vessels. A localized basal arachnoiditis from substances foreign to the normal CSF may also occur, causing obstruction to CSF drainage (2,11).

In spinal column tumors increased CSF protein appears to be a major factor causing increased intracranial pressure and papilledema, frequently through the development of a communicating hydrocephalus. Elevated CSF protein probably also plays a role in the Guillain-Barré syndrome and poliomyelitis (5). Experimentally, serum protein and artificially viscous solutions placed in the CSF have been shown to decrease the rate of fluid absorption from the subarachnoid space (5). Cerebrospinal fluid viscosity and osmotic tension themselves seem to be less important, as their effect should be stable over time. Impaired CSF absorption in a patient with hydrocephalus from a lumbar neurofibroma was demonstrated using CSF infusion studies (8), supporting these experimental studies.

This case illustrates the syndrome of papilledema associated with an intradural tumor, in this instance a cauda equina paraganglioma. The visual symptoms and papilledema responded well to resection of the lesion. The increased intracranial pressure is possibly caused by blockage of the outflow channels by increased protein in the CSF, although hydrocephalus was not present. Magnetic resonance imaging of the lumbosacral region now allows this diagnosis to be recognized with little risk to the patient.

REFERENCES

We present two cases of degenerative myopia with abduction deficiency. Three mechanisms can explain the defect in the abduction: (a) the size of the long globe filling the space of the orbits, (b) the tightness of the medial recti due to long axis of the globe, and (c) longstanding esotropia becoming decompensated later in life. We believe that high myopia is not a well-known cause of abduction deficiency, and it should be considered in the differential diagnosis.

Key Words: Orbit—High myopia—Abduction deficiency—Motility disorders.

CASE REPORTS

Case 1

A 47-year-old woman presented with the complaint of limitation of eye movements, which worsened for the past 2 months. She had no diplopia.

On examination visual acuities were 20/400 in the right eye and 20/200 in the left eye with -23 (+1.00 x 90°) and -20 (+1.00 x 90°) correction, respectively. Color vision was 15/15 bilaterally. Ophthalmoscopy revealed bilateral degenerative myopic changes, including peripapillary hypopigmentation and peripheral pigmentary degeneration. Both pupils were isocoric and equally reactive to light. Visual fields with confrontation were full. On primary gaze she was 40 diopters esotropic. She had an abduction deficiency in both eyes (90% of normal in OD, and 70% in OS), also her upgaze was slightly limited (Fig. 1). A Hertel exophthalmometry measurement was 20 mm bilaterally with a base of 122 mm. Her intraocular pressures with applanation were 19 mmHg bilaterally and did not increase with upgaze. Her thyroid tests were normal. An orbital computed tomography (CT) showed bilateral orbits filled by the globes with no thickening of extraocular muscles (Fig. 2). Length of the globe was 35 mm OD and 33.7 mm OS,
measured by axial orbital CT. Tensilon test was negative. She was otherwise healthy and denied any trauma, hypertension, diabetes mellitus, or thyroid disease. She had undergone a strabismus surgery for cosmetic reasons, during which both medial recti were found to be tight. Forced-duction test done at the time of surgery showed bilateral restriction in abduction. A 5-mm recession to medial rectus and 6-mm resection to lateral rectus procedure was carried out to left eye.

Case 2

A 40-year-old man presented with horizontal diplopia for 20 years. His visual acuities were 20/100 (−11.0) OD, and 20/40 (−9.0) OS. His color vision, intraocular pressure, and visual fields were normal. He had degenerative myopic changes with large posterior staphyloma in his fundi. Both pupils were isocoric and equally reactive to light. Hertel exophthalmometry measured as 19 mm in both eyes with the base of 115 mm. There was no increase in intraocular pressure on attempted upgaze. There was bilateral abduction deficit (80% of normal) with a left inferior oblique overaction (Fig. 3). CT scan of the orbit showed globes with right posterior staphyloma, and without thickening of extraocular muscles (Fig. 4). Length of the globe was 36.7 mm OD, 38.5 mm OS measured by axial orbital CT. His thyroid tests were within normal limits. Tensilon test was negative, whereas the forced-duction test revealed restriction in abduction. Fresnel prisms were prescribed for his diplopia.

COMMENTS

The possibility of bilateral sixth nerve palsy has been ruled out in our case by positive forced-duction test.

The most common cause of restrictive gaze deficiency is thyroid eye disease with thick muscle
bellies in CT scan (2). It has been reported previously that high myopia and endocrine ophthalmopathy may coexist (3). We believe that we have excluded this probability as well as myositis with normal extraocular muscle morphology in CT scanning.

Three mechanisms can explain the abduction deficiency in our patients with high myopia. The first is that the long globe filling the space of the orbits may cause mechanical limitation in the ocular movements more prominent in adduction as in Case 1. High myopia as a cause of restrictive motility disturbance has been reported previously (4).

The second mechanism may be the tightness of the medial recti due to long axis of the globe (N: 23.5–25.5 mm) causing limitations, especially in the abduction. This can explain the abduction deficiency in both patients. Also, it has been postulated that the medial rectus has abnormal insertion in patients with esotropia and myopia (5).

Lastly, long-standing esotropia may cause foreshortened medial rectus bilaterally, and esotropia may become decompensated later in life.

These two cases suggest that high myopia should be considered in the differential diagnosis of restrictive abduction deficiency.

REFERENCES

Editorial Comment

High Myopia Causing Bilateral Abduction Deficiency

The preceding report by Aydin et al., describing two cases of high myopia associated with progressive esotropia and abduction deficiency, is an important addition to the neuro-ophthalmology literature. The late Philip Knapp described this condition some 15 years ago in a group of Jewish women patients whom he treated. I have had a number of patients (though not Jewish) with a similar condition. All have been female. They develop thyroid-like tight medial rectus with progressive esotropia. The differential diagnosis from thyroid disease in those PTS is difficult. I have learned to be very cautious in prognosticating for them, as they have a strong tendency to recur, following surgical correction and the like.

This paper draws attention, in the neuro-ophthalmological community, to an entity with which pediatric ophthalmologists, on the whole, are familiar. There is no need for an extensive workup in these patients; a good office examination, forced ductions in the presence of high myopia, are all that is necessary to make the diagnosis. Surgical prognosis should be guarded.

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Interstitial Keratitis and Iridoschisis in Congenital Syphilis


Bilateral interstitial keratitis and iridoschisis are reported in four cases with extraocular stigmata of congenital syphilis and positive syphilis serology. The iridoschisis was extensive in two cases giving the iris an unusual ragged appearance, while it was slight in one case. Iridoschisis may suggest the diagnosis of congenital syphilis, especially when interstitial keratitis is mild. Chronic open-angle glaucoma should be excluded in all patients with interstitial keratitis and iridoschisis.

Key Words: Congenital syphilis—Interstitial keratitis—Iridoschisis.

Acquired syphilis remains an important cause of neuro-ophthalmic disease, with more than 48,000 cases reported in the United States in 1990 (1), of which it is estimated that 10% of untreated cases develop neurological disease (2). Less emphasized in recent years are the difficulties that elderly patients experience from the stigmata of congenital syphilis. While interstitial keratitis and chorioretinal scarring are well recognized and may cause reduced visual acuity and visual field defects (3), other features, including recurrent anterior uveitis (3), steroid-induced uveitis (4), cataract (3, 5), band keratopathy (3, 5), keratoconus, and chronic open-angle glaucoma (5, 6), have been reported. Several isolated cases of iridoschisis have also been described (7), but only recently has an association between interstitial keratitis and iridoschisis in congenital syphilis been proposed (8, 9). We report a further four such cases, and emphasize the apparent high incidence of chronic open-angle glaucoma in these patients.

CASE REPORTS

Case 1

A 51-year-old woman gave a history of poor visual acuity as a child, attending a school for the partially sighted from the age of 16 years. Her right eye was profoundly amblyopic, and a large-angle right esotropia was corrected when she was 8 years old, and a secondary right exotropia was corrected when she was 43.

She had normal facies but characteristic Hutchinson's teeth. Right visual acuity was CF at 1 m and left 20/200. There was severe scarring of the left cornea with both patent and ghost vessels secondary to interstitial keratitis, which was mild in the right eye. Both anterior chambers were quiet, and there were no keratoprecipitates. There was atrophy of the stroma of the anterior stromal leaf of
both irides with preservation of radial fibers (Fig. 1). The posterior iris stroma was well preserved (Fig. 2), and there was no iris retroillumination. Right intraocular pressure was 15 mmHg and left 16 mmHg, and gonioscopy showed grade 2 open anterior chamber angles in both eyes, with moderate pigment deposition but no peripheral anterior synechiae. Pupil responses were normal, and there was no relative afferent pupillary defect. There was bilateral chorioretinal scarring and optic atrophy. Treponema pallidum hemagglutination (TPHA) and fluorescent treponemal antibody absorption (FTA-Abs) were positive (Table 1).

Case 2

A 70-year-old woman complained of reduced vision in both eyes for 6 months. At age 20 she had presented with bilateral interstitial keratitis, which resolved spontaneously, but profound sensorineural deafness developed 10 years later. A Wasserman reaction was positive, and she was treated with intramuscular penicillin. Chronic open-angle glaucoma had been diagnosed at age 60, but intraocular pressures were normalized, and visual field loss and pathological disk cupping halted on topical antiglaucoma therapy.

On examination, there was maxillary hypoplasia and an absent nasal bridge, and she was profoundly deaf. Right visual acuity was 20/80 and left 20/60. Slit lamp examination showed diffuse bilateral interstitial keratitis with central corneal thinning and prominent ghost vessels. Both anterior chambers were quiet and there was no iris retroillumination. The substance of the anterior stromal leaf of the iris was lost in the right eye with preservation of radial fibers extending from the iris root to the pupillary margin. There was mild iridoschisis in the left eye. Right intraocular pressure was 18 mmHg, left 18 mmHg, and gonioscopy showed a limited view of an open-angle with moderate pigment deposition and no peripheral anterior synechiae. Pupil responses were normal and there was no relative afferent pupillary defect. Fundal examination showed bilateral glaucomatous optic disk cupping, but normal retinas. Despite reduced visual acuity, visual field examination showed constriction of both visual fields. TPHA and FTA-Abs were positive (Table 1).

Case 3

A 73-year-old woman complained of poor visual acuity. On entering military service 48 years previously, best corrected visual acuity was right and left 20/60. A year later she experienced an acute episode of bilateral interstitial keratitis, after which her visual acuity further deteriorated. She had no systemic stigmata of congenital syphilis.

**TABLE 1.**

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Right visual acuity was 20/80 and left 20/200. There was marked interstitial keratitis with prominent ghost vessels in both eyes (Fig. 3). The right iris showed patchy loss of the anterior stromal leaf with relative preservation of radial fibers (Fig. 4). The left iris showed similar changes confined to the lower half of the iris. Right and left intraocular pressures were 16 mm Hg. Both pupils were irregular, but there was no relative afferent pupillary defect. There was nuclear sclerosis in the left eye, bilateral chorioretinal scarring, and slight pallor of both optic nerve heads. A left penetrating keratoplasty with extracapsular cataract extraction was performed without complication. At 6 months, left visual acuity had improved to 20/120. Syphilis serology was positive (Table 1).

Case 4

A 75-year-old woman with congenital deafness gave a 24-year history of bilateral chronic open-angle glaucoma. Intraocular pressures were normalized with topical antiglaucoma medication for 10 years, before intraocular pressures rose to above 50 mm Hg on full topical therapy and systemic acetazolamide. Uncomplicated trabeculectomy was performed in the right and then the left eye. Intraocular pressures remained normal on no additional medical therapy for 14 years. Right extracapsular cataract extraction and penetrating keratoplasty were performed 10 years after the original surgery when marked nuclear sclerosis developed in the right eye.

Right visual acuity was hard movements (HM) and left 20/200. A clear, penetrating keratoplasty was noted in the pseudophakic right eye. Interstitial keratitis and old keratoprecipitates were present in the left eye. The right iris was normal, but the left eye showed mild loss of the anterior stromal leaf in the ciliary portion of the inferior iris. Right intraocular pressure was 16 mm Hg, and left 5 mm Hg, and gonioscopy showed grade 2 open anterior chamber angles with mild pigment deposition. Pupil responses were normal, and there was no relative afferent pupillary defect. There was a small right Nd:Yag posterior capsulotomy and moderate nuclear sclerosis in the left eye. There was a right macular scar. The inferior rim of the right optic disk was notched and corresponded to a large right superior arcuate scotoma. Right and left cup to disk ratio was 0.5. Bilateral inferonasal chorioretinal scarring was present. TPHA and FTA-Abs were positive (Table 1).

DISCUSSION

We report four cases of congenital syphilis, three of which had well-recognized extraocular stigmata and all of whom had positive syphilis serology (10). Interstitial keratitis was present in all cases; prominent ghost vessels were present in two cases, and one case had significant stromal thinning. Presentation of two patients with interstitial keratitis at ages 20 and 26 was typical and common when congenital syphilis was more frequently encountered (5). Iridoschisis involving predominantly the inferior half of the iris was present in all cases (7). Preservation of anterior stromal leaf radial fibers and deep stromal iris tissue without transillumination were all characteristic findings.
Correctopiae and ectropion uveae were absent (7). Despite difficulties with gonioscopy, no peripheral anterior synchiae or fibrovascular membranes were seen to account for the open-angle glaucoma that developed in Cases 2 and 4. This was unusual, in that a narrow-angle and peripheral anterior synchiae are well reported in large series of cases of interstitial keratitis (5), although they presumably represent more severe cases, and it is possible that at least two of our cases were mild, in that the patients could not remember the clinical episode.

The association of interstitial keratitis and iridoschisis has only been reported in individual cases before. While interstitial keratitis is a common manifestation of congenital syphilis, iridoschisis has rarely been reported, although difficulty in visualizing the iris in cases with interstitial keratitis may in part explain this. The fact that we have identified four cases suggests the association may be more common than is generally realized. Neither interstitial keratitis nor iridoschisis have a suppurative component, and both are presumably immunologic in their pathogenesis. Changing levels of antigen in patients with congenital syphilis may explain the frequent delayed onset of interstitial keratitis. Some cases of interstitial keratitis are reported after the onset of treatment, suggesting that dead tissue antigen or protein may suddenly be released from the corneal stroma into the limbal vascular arcades and play a significant role in precipitating the disease. The fact that the intact blood-aqueous barrier prevents many proteins from coming into contact with iris stroma perhaps explains the less common incidence of iridoschisis.

Two of our cases had chronic open-angle glaucoma, eventually requiring trabeculectomy. In both cases the anterior chamber angle was grossly normal with no peripheral anterior synchiae or visible fibrovascular membrane. Chronic open-angle glaucoma with isolated iridoschisis in the absence of peripheral anterior synchiae or apparent angle pathology is well reported and the etiology remains obscure. It is presumed that an as yet unrecognizable abnormality exists within the trabecular meshwork, although this has not been confirmed histologically.

There may be an association between interstitial keratitis and iridoschisis in congenital syphilis. This is an important association to be aware of because, in cases in which interstitial keratitis is mild, iridoschisis may suggest the diagnosis of congenital syphilis. Chronic open-angle glaucoma would appear to be a sequela of this association due to a presumed abnormality of the trabecular meshwork. We emphasize the need for glaucoma to be excluded in cases of interstitial keratitis and iridoschisis.

Acknowledgments: We would like to thank Mr. Awdry and Mr. Cheng for allowing us to report their patients.

REFERENCES

Neuroretinitis Due to Seronegative Syphilis Associated with Human Immunodeficiency Virus

Lawrence S. Halperin, M.D.

Syphilis serologic testing is felt to be extremely reliable. A case of syphilitic neuroretinitis is reported where serologic testing was negative due to human immunodeficiency virus infection. A prompt response to high-dose intravenous penicillin was achieved.

Key Words: Neuroretinitis—Seronegative syphilis—Human immunodeficiency virus.

CASE REPORT

A 31-year-old bisexual man presented with 3 days of painless, severe, bilateral visual loss. Conjunctivitis developed 5 days earlier, and 2 days earlier he had bilateral visual loss. He had a history of treated gonorrhea, and he may have had contact with syphilis but had a negative serology.

Vision was RE counting fingers, LE 20/200. Pupils were sluggish. He had moderate, bilateral conjunctivitis, a quiet anterior chamber, and no keratic precipitates. Moderate vitritis was present in both eyes. Fundus examination showed bilateral, severe optic nerve swelling with flame hemorrhages and peripapillary serous elevation of the retina. A stellate pattern of hard exudate was present in the macula (Fig. 1). He had cervical lymphadenopathy.

FIG. 1. Photograph of right eye demonstrating disk edema, peripapillary hemorrhages, and serous elevation of the macula with hard exudate. Vision was count fingers.
Photograph of right eye showing decrease of disk edema and hemorrhages. The elevation of the macula is gone and the amount of hard exudate has increased. Vision was 20/30.

A complete blood count was normal, except for a hemoglobin of 13.2. Serum chemistries, chest x-ray, and computed tomography scan of the head and orbits were within normal limits. A VDRL and fluorescent treponemal antibody absorption (FTA-ABS) were nonreactive. A serum IgG antibody titer for the varicella zoster virus was slightly elevated. Cerebrospinal fluid evaluation revealed one lymphocyte, a protein of 62 (elevated), a glucose of 70 (elevated), and a nonreactive VDRL. Human immunodeficiency virus enzyme-linked immunosorbent assay (ELISA) and Western blot were both positive. Lyme titers were negative.

The patient was started on 2 million units of intravenous penicillin every 4 hours for a presumptive diagnosis of syphilis. In 3 days, vision was RE 20/40, LE 20/40. The optic disk edema and serous retinal elevation had decreased. The amount of hard exudate increased as the fluid was absorbing (Fig. 2).

After 14 days of penicillin, 18 million units a day, vision was 20/30 in both eyes and the clinical examination markedly improved.

DISCUSSION

This patient was started on high-dose intravenous penicillin on the clinical suspicion that syphilis was the cause of the optic nerve and ocular inflammation. The patient was monitored carefully for a clinical response to penicillin, and, if the visual acuity had not improved in 2 to 3 days, other diagnoses and treatments would have been considered.

Syphilis is a well-known cause of optic neuritis and visual loss. A stellate pattern of exudate centered on the foveola with disk edema has been described (1). There have been several reports concerning syphilis and acquired immunodeficiency syndrome (2–4). All of these cases had positive serologic testing of the serum and/or cerebrospinal fluid. Most responded extremely well to high-dose, intravenous penicillin.

This case is unique in that all serologies were negative. Haas et al. (5) found that 7% of patients asymptomatic and 38% symptomatic for human immunodeficiency virus (HIV positive) became seronegative to syphilis testing. Hicks et al. (6) reported one patient with human immunodeficiency virus infection, who required skin biopsy to demonstrate spirochetes, as all serologic tests were repeatedly negative (6).

REFERENCES

Prolonged Course of Bilateral Acute Idiopathic Blind Spot Enlargement

Michael Lee Cooper, M.D., Ph.D. and Robert L. Lesser, M.D.

We report a patient with bilateral "acute idiopathic blind spot enlargement" (AIBSE) in whom visual symptoms and enlarged blind spots persisted for over 6 years and preceded the development of peripapillary hyperfluorescence on fluorescein angiography. These findings confirm the prolonged course that AIBSE can sometimes take and the suggestion that this rare disorder is due to peripapillary retinal dysfunction. Key Words: Acute idiopathic blind spot enlargement—Peripapillary retinal dysfunction.

Blind spot enlargement in the absence of optic nerve dysfunction is most often associated with papilledema due to increased intracranial pressure. However, enlargement of the blind spot without disk swelling has been found in "acute idiopathic blind spot enlargement" (AIBSE) (1), which, in some cases, is associated with multiple evanescent white dot syndrome (MEWDS) (2-5). These big blind spot disorders are usually transient and unilateral; their etiologies are unknown.

We describe a case of AIBSE in which blind spot enlargement occurred simultaneously in both eyes and persisted for over 6 years; this enlargement preceded peripapillary angiographic changes. Our patient also had laboratory findings suggestive of syphilis.

CASE REPORT

A 39-year-old white woman was well until January 1984, when she developed continuous scintillations described as "pinwheels" and "silver flashing circular images" located in the area of the blind spot in each eye. The patient had no other associated symptoms. She had had genital herpes in 1976. The patient had traveled to Zaire, Brazil, and Afghanistan in the preceding 7 to 10 years.

Examination by the patient's private ophthalmologist within 3 weeks of symptom onset revealed vision of 20/20 OU with bilateral tilted disks and enlarged blind spots on Goldmann field testing. Neurological evaluation 6 weeks later was unremarkable except for the visual field changes.

We examined the patient in April 1984. Her best corrected visual acuity was 20/20 in each eye (-3.25 - 1.25 × 10° OD; -4.50 -1.25 × 10° OS). HRR color vision, extraocular motility, cranial nerve testing, slit lamp examination, and intraocular tensions were all within normal limits. The pupils were 2 mm on the right and 2.5 mm on the
left, but there was no ptosis and the cocaine test was negative. Goldmann visual fields showed marked enlargement of the blind spots, right greater than left, with full peripheral fields (Fig. 1). Examination of the fundi revealed no abnormalities except slight tilting of the right disk and marked tilting of the left disk. No disk edema or macular pathology could be seen. Fluorescein angiography showed hyperfluorescence around the right disk with areas of blocked fluorescence; there was no staining or leakage. The left posterior pole was within normal limits angiographically (Fig. 2A,B). The electoretinogram was normal.

Routine urine and blood chemistries and hematologic studies were normal, as were thyroid and liver function tests, serum folate and vitamin B12, angiotensin-converting enzyme, serum lysozyme, urine heavy metal screen, and erythrocyte sedimentation rate. Serum protein electrophoresis (SPEP), purified protein derivative, anti-nuclear antibody, rheumatoid factor, and serum VDRL were negative. Serum immunoelectrophoresis

FIG. 1. Goldmann visual fields showing marked enlargement of both blind spots. (A) Left eye; (B) right eye. These fields were unchanged over the course of 6 years.
showed no monoclonal spike, although the IgM was moderately elevated and albumin moderately decreased. The chest x-ray was normal. EEG and triple evoked responses were normal except for an abnormal pattern visual evoked response in the right eye, felt to be consistent with right optic nerve or retinal dysfunction.

During the 5 months following her onset of symptoms, the patient had normal contrast computed tomography scans of the brain and sellar region. Five lumbar punctures were performed during this time, showing normal protein, glucose, albumin, and opening pressure. The VDRL was negative on each tap. Three to four oligoclonal bands of moderate intensity were seen on one examination. The cerebrospinal fluid (CSF) IgG was elevated (5.2 to 7.1 mg%; upper limit of normal 3.5), as was the IgG/albumin ratio (0.3 to 0.4; upper limit of normal 0.18). Although the cell count was normal on the first two taps, slight pleocytosis was noted on the last three in June 1984, with 16 to 20 white cells on each tap (4 to 26% monocytes and the rest nonmonoclonal lymphocytes). CSF cytology was negative for malignancy. CSF cultures were negative.

The serum VDRL was nonreactive; however, the serum fluorescent treponemal antibody absorption (FTA-ABS) was positive. The testing laboratory considered the FTA-ABS to be definitely positive and not an atypical test result; a borderline Lyme IgG titer (1:200) was felt to represent a cross-reaction. Extensive serological studies for other infectious agents were within normal limits. The T-4:T-8 lymphocyte ratio was normal.
Because of the positive FTA-ABS, the patient received penicillin G (5 million units i.v. q6h) for 10 days, followed by 3 weekly injections of 2.4 million units of i.m. benzathine penicillin. Repeat blood VDRL and FTA-ABS were both negative at the time antibiotics were started in late June 1984, and repeat lumbar puncture at that time showed a negative VDRL, with the white blood cell count having decreased to two.

Shortly after completing her treatment, the patient was lost to follow-up. She was examined again in March 1990, when she reported persistence of her visual symptoms. Her best corrected acuity was 20/20 -2 OD and 20/25 +2 OS. Her pupillary responses and color vision were normal, and Goldmann fields showed enlarged blind spots unchanged from 1984. However, fundus examination showed some increased peripapillary hyperfluorescence (Fig. 2C,D). The electroretinogram was again unremarkable. The patient stated that she had never had a follow-up lumbar tap; a repeat FTA-ABS was negative.

DISCUSSION

Fletcher et al. (1) recently described seven patients who had “acute idiopathic blind spot enlargement” (AIBSE). These young, typically female patients had monocular blind spot enlargement and positive visual phenomena (e.g., photopsias) without disk edema; visual acuities and color vision were normal. All the patients had resolution of symptoms within 2 to 3 months, and visual fields in three patients showed normal blind spot size within 1 year. Our patient had simultaneously bilateral AIBSE, with a pattern similar in many respects to the patient of Wakakura and Furuno (6) and to case 3 of Singh et al. (7). These latter two patients also showed bilateral blind spot enlargement and peripapillary hyperfluorescence 4 to 5 years after the onset of symptoms. However, while the patient of Wakakura and Furuno did have simultaneous bilateral involvement, 4 years elapsed before the development of symptoms in the second eye of the case in Singh et al. (7).

Two of Fletcher et al.’s (1) AIBSE patients had prolonged photostress recovery tests, and, although fluorescein angiography was reported as normal, multifocal electoretinography done in two patients was abnormal around the disk. Four of the original AIBSE patients had positive visual symptoms in the area of the enlarged blind spot, and all had an absolute scotoma with steep borders. Fletcher et al. (1) concluded that these findings were consistent with peripapillary retinal dysfunction rather than optic nerve disease.

While peripapillary myopic degeneration and primary choroidal atrophy can produce enlarged blind spots, we feel it unlikely that such etiologies account for the findings in our patient. These processes are felt to begin in the retinal pigment epithelium (RPE) or, more likely, the choroid, with retinal changes occurring secondarily (8-10). However, in our patient the left blind spot enlargement preceded any angiographic abnormalities; furthermore, the left eye was the more myopic (11), but the angiogram was initially abnormal only in the right. The fact that visual symptoms and blind spot enlargement preceded angiographic abnormalities in our patient’s left eye supports the contention that AIBSE is due to peripapillary retinal dysfunction.

The finding that blind spot enlargement preceded the development of peripapillary atrophy in our patient’s left eye is also significant because it suggests either a marked delay in the depigmentation of the affected pigment epithelium or that the patient had further episodes of AIBSE affecting the RPE of this eye. It does not seem likely that the patient had a recurrence of AIBSE since, although she reported persistence of symptoms for 6 years, she had no period of increased symptoms. Moreover, the left blind spot was no larger after 6 years than at the time of initial presentation, although one would expect additional enlargement of the blind spot in the case of recurring disease. Thus, in the absence of evidence suggesting exacerbation of the disease, we believe our case demonstrates that RPE damage in AIBSE may take many months, or possibly even years, to become apparent.

It has been suggested (2-5,12) that the patients of Fletcher et al. (1) and of Wakakura and Furuno (6) actually represent late cases of multiple evanescent white dot syndrome (MEWDS). MEWDS (13-15) also typically occurs in young healthy individuals, and presents with visual loss, scotomata, and multiple white lesions in the RPE or deep retina of the posterior pole. The fundus lesions resolve in a few weeks, although photopsias and blind spot enlargement can occasionally persist. However, it seems unlikely that all cases of AIBSE are secondary to MEWDS, since a number of AIBSE patients seen shortly after symptom onset have shown no evidence of this second disorder (1,6,7). Indeed, Singh et al. (7) consider AIBSE to be a disease spectrum in which MEWDS is one type.

While we cannot state with certainty that our
patient did not initially have fundus findings of MEWDS, no such lesions were seen by an ophthalmologist within several weeks of symptom onset. In addition, MEWDS is not known to be associated with CSF pleocytosis (Dr. L. Jampol, personal communication). The patient’s positive FTA-ABS, elevated CSF IgG, and CSF pleocytosis suggest that she had neurosyphilis (16), and it is known that syphilis can cause neuroretinitis. Although Lyme disease can also have neurologic and ophthalmic findings, this disease does not seem a likely etiology in the present case. Our patient’s Lyme titer was only borderline, and she had no other typical findings of Lyme disease, such as erythema chronicum migrans, constitutional symptoms, or arthritis.

While the FTA-ABS false-positive rate is less than 1% (17), we cannot state with certainty that our patient did indeed have syphilis, because two repeat FTA-ABS tests were negative. Further, even if the patient definitely had syphilis, her AIBSE could have been unrelated to this. In any event, the present case suggests that obtaining spirochetal serologies may be of benefit in future attempts to characterize AIBSE. Further, our patient is unusual even for this uncommon disorder, given her simultaneous bilateral involvement, prolonged course, and delayed onset of peripapillary angiographic changes.

REFERENCES
Aneurysmal Oculomotor Nerve Palsy in an 11-Year-Old Boy

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Cerebral aneurysms are rare in children. When they occur, they usually present with a history of subarachnoid hemorrhage. Gabianelli et al. (1) recently reported a 14-year-old girl with an isolated oculomotor nerve palsy due to aneurysm. In their discussion, they state that arteriography is, “Unnecessary in patients under 10 (years of age) if the symptoms and signs of subarachnoid hemorrhage are absent or high resolution computerized tomography scan or adequate magnetic resonance imaging scan is normal.” To date, their patient is the youngest reported in the literature with an isolated oculomotor nerve palsy proved to be caused by cerebral aneurysm. We report herein an 11-year-old boy who presented with an oculomotor nerve palsy due to aneurysm with minimal preceding symptoms and no other signs of intracranial disease.

Key Words: Cerebral aneurysm—Third (or oculomotor) nerve palsy in children.

CASE REPORT

An 11-year-old boy had diarrhea, which spontaneously resolved. Seven days later, he experienced dizziness and vertigo and reported ringing in both ears. Then mild ptosis appeared in his right upper eyelid, which was accompanied by pain in the right orbit. He also had nausea and vomiting, but this resolved within 3 days. However, his headache persisted, and he developed a right oculomotor nerve palsy. He was treated concurrently with oral penicillin for otitis media by another physician without improvement.

Three weeks after the onset of symptoms, the patient was admitted to the hospital for evaluation. Examination at that time revealed an alert child with measured visual acuity, right eye 20/30, left eye 20/20. Visual fields by confrontation were normal. The right pupil measured 5 mm and was sluggishly reactive. The left pupil measured 3 mm and was briskly reactive. No afferent pupillary defects was detected.

Motility examination revealed an exotropia and right hypertropia associated with incomplete right oculomotor nerve palsy (Fig. 1). Neurological examination was otherwise normal and without evidence of meningeal irritation. Computed tomography of the head and orbits, with contrast and 5-mm axial sections, was performed the day after admission and was normal, with no focal mass effect or shift of the midline. Serial images through the orbit or sella showed no abnormality. The working diagnosis was ophthalmoplegic migraine. On the second hospital day, the patient developed nausea, vomiting, and complained of a throbbing right-sided headache. A lumbar puncture had an opening pressure of 120 cmH2O. Examination of the cerebrospinal fluid revealed 75 red blood cells
FIG. 1. Partial right 3rd nerve palsy in an 11-year-old boy.

and 2 white blood cells/1 cm, with 71 mg% glucose. Because of the abnormal cerebrospinal fluid, angiography was performed and revealed an aneurysm of the right internal carotid artery at the origin of the posterior communicating artery (Fig. 2). The patient subsequently underwent surgery to clip the aneurysm. Postoperatively, visual acuity was 20/50 in the right eye. No afferent pupillary defect was noted. Repeat angiography 1 week postoperatively was indicative of a moderate degree of spasm of the internal carotid artery. Motility showed complete ptosis OD with exotropia and hypotropia, showing complete paralysis of the 3rd cranial nerve. The patient was subsequently lost to follow-up.

FIG. 2. Angiography demonstrates an aneurysm of the right internal carotid artery at the origin of the posterior communicating artery (arrow).

DISCUSSION

Although the history given by this patient may have suggested subarachnoid hemorrhage, at the time of presentation, he was alert, oriented, and free of suspicious systemic signs or symptoms. The only important physical finding on ophthalmologic and neurologic examination was a right oculomotor 3rd nerve palsy. The mildly decreased acuity could be explained by lenticular aberration from a dilated pupil. One could argue, therefore, that this was an isolated cranial mononeuropathy. Most authors seem to use the term “isolated” to refer to limited signs and symptoms at the time of examination. Our patient would thus appear to fit into this category. His aneurysm was not detected on the computed tomography scan. This might have been because this older generation scan was done with 5-mm slices. However, conventional angiography is still necessary for aneurysm detection and delineation when this diagnosis is suspected (1).

Miller (2) reports on 30 children with isolated oculomotor nerve palsy. Two patients (ages 16 and 17) with aneurysms are described. Both had preceding symptomatology consisting of occipital and deep orbital headache, nausea, vomiting, and stiff neck. In an editorial on Gabianelli’s recent
report, Fox (3) suggests that further unreported cases concerning this issue will be brought to light.

At age 11 years, we believe ours to be the youngest patient reported to date with an essentially isolated 3rd nerve palsy due to a cerebral aneurysm. We therefore believe that age alone should not be considered a cutoff for the need for angiography in a patient with an otherwise isolated oculomotor nerve palsy. Angiography should be performed in any case where an aneurysm would otherwise be present in the differential diagnosis.

REFERENCES
Absence of the Relative Afferent Pupillary Defect with Monocular Temporal Visual Field Loss

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We report five patients with monocular temporal visual field abnormalities who did not have clinically detectable relative afferent pupillary defects. The causes for the field defects were posterior ischemic optic neuropathy, craniopharyngioma, pituitary adenoma, pseudotumor cerebri, and traumatic optic neuropathy. We discuss the possible explanations for our observations, considering the known anatomy of the pregeniculate visual pathways and the afferent pupillary pathways.

Key Words: Relative afferent pupillary defect—Monocular temporal visual field loss.

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The relative afferent pupillary defect (RAPD) is the most objective and reliable sign of asymmetric dysfunction of the anterior visual pathways. The depth, or magnitude, of the RAPD is apparently correlated with the amount of visual field loss (1). Indeed, monocular visual field defects without an RAPD are considered a sign of hysteria or malinger by some authors (2–3). In rare instances, completely monocular temporal visual field defects have been described with mass lesions (4–8), posterior ischemic optic neuropathy (9), optic neuritis (10), retinal degenerations (11), and the empty sella syndrome (12–14). In most of these cases RAPDs were found.

We report five patients, with either complete or incomplete monocular temporal visual field defects, who did not have clinically detectable RAPDs (Table 1). This observation led us to reexamine the traditional thinking about retinotectal afferent pupillary pathways and the relationship between monocular visual field loss and RAPDs.

METHODS

This study consisted of a thorough evaluation of five patients with monocular temporal visual field defects, either complete or incomplete, not associated with a relative afferent pupillary defect. The visual acuities, visual fields, fundus appearance, RAPD and neuroimaging studies were evaluated. Visual acuity was measured by Snellen optotypes. Visual fields were done kinetically by the Goldmann technique (all patients), or by threshold static testing with the Humphrey visual field analyzer as well (patient 1). The RAPD was tested by using an indirect ophthalmoscope at highest intensity while the patients fixated a distance target.
Radiologic studies included intravenous digital subtraction angiography (IV DSA; patient 1), computed tomography (CT) of the head (all patients), and magnetic resonance imaging (2 patients).

**CASE REPORTS**

**Case 1**

In July 1985, L.P., a 55-year-old man with a history of severe coronary artery disease, had an episode of severe headache with complete blindness lasting 30 minutes and resolving completely. Intravenous digital subtraction angiography done shortly afterward showed only a small amount of calcification at the origin of the left internal carotid artery.

In December 1985, he suddenly and permanently lost vision in the entire temporal field of the left eye. Computed tomography of the head was normal. Neuro-ophthalmologic examination revealed right eye vision of 20/20 +3 and 20/25 left eye vision. A relative afferent pupillary defect was not noted on this or subsequent examinations. Pupillary size under direct illumination was equal; that is, Kestenbaum's number (16) was zero (Fig. 1A-C). Funduscopy showed a cholesterol embolus in the inferotemporal artery OS; optic atrophy was not noted and the right eye was completely normal except for mild nuclear lens sclerosis. Visual field testing by Humphrey (Fig. 2A,B) and Goldmann techniques (Fig. 3A,B) showed a complete monocular temporal hemianopia in the left visual field. Duplex carotid sonography done in November 1986 showed evidence of plaque formation at the origins of both internal carotid arteries but less than 20% stenosis. Visual fields and pupillary examination were unchanged as of April 1987.

**Case 2**

A 19-year-old black man (K.B.) was first evaluated on June 15, 1989 because of difficulty with distance vision. He had a craniopharyngioma operated on in early 1988. Best corrected visual acuity was 20/30 with the right eye and 20/20 with the left eye. Pupillary examination revealed 1 mm of anisocoria with brisk direct reactions. There was no relative afferent pupillary defect clinically. Ocular motility was normal. Dilated fundus examination showed bilateral optic atrophy, more marked on the right. The right visual field had a temporal hemianopic defect (Fig. 4A), whereas the left visual field was within normal limits (Fig. 4B). On 11/3/89 he was reexamined and had bitemporal visual field loss due to recurrence of the tumor. A 0.9 log unit RAPD was present OD (17).

**Case 3**

D.C. was a 51-year-old woman last examined in November 1988. She was status postsurgery for removal of a pituitary adenoma. Vision with the right eye was 20/20 – 3 and was 20/40 with the left eye. Visual fields revealed a left temporal hemianoptic scotoma as well as depression of the left superotemporal isopters (Fig. 5B). Visual field testing of the right eye was normal (Fig. 5A), and a relative afferent pupillary defect was not detected.

**Case 4**

A 38-year-old woman (D.S.) was followed serially for pseudotumor cerebri, and was last examined in August 1989. Visual acuity was to 20/15 with each eye, and color vision was normal by pseudoisochromatic color plates. Numerous visual fields by the Goldmann technique showed consistent depression of the inferotemporal isopters on the right only (Fig. 6A,B). Mild postpapilledema optic atrophy was present in the right eye; the left optic disk was flat and spontaneous venous pulsations were present bilaterally. An RAPD was not detected on this or any previous examinations.

**Case 5**

A 27-year-old woman involved in an automobile accident on May 27, 1985, suffered a closed head injury with traumatic right optic neuropathy. An inferotemporal scotoma has persisted in the right visual field (Fig. 7A,B). Best corrected acuity was 20/30 – 2 with the right eye and 20/15 with the left eye, without evidence of a relative afferent pupillary defect. Computed tomography of the head was normal.

**Discussion**

Chiasmal visual field defects are typically temporal, but may be junctional as described.
brand and Saenger (18) and Traquair (4,10), and are most often caused by mass lesions. Monocular temporal hemianopic defects, whether complete or incomplete, are equally important because they have the same localizing significance (7,8,10,18).

The topographic anatomy of the optic nerve fibers in the anterior visual pathways, projecting from the retinal ganglion cells to lateral geniculate body, is understood. Macular fibers, especially the papillomacular bundle, in primates and man, are located temporally in the optic disk and distal optic nerve, but come to occupy a large central portion of the more proximal optic nerve near the chiasm (19). The upper macular fibers cross dorsally in the chiasm, and the lower macular fibers cross ventrally. The extramacular fibers from more peripheral retinal ganglion cells remain peripheral in the optic nerve and cross anteriorly in the chiasm (19, p. 387). The more ventrally placed crossed fibers, predominantly from inferior retina subserving supertemporal visual field, loop anteriorly in the contralateral distal optic nerve as far as 3 or 4 mm, before turning back toward the lateral geniculate nucleus. This fiber path was initially termed the "commissura arcuata anterior" by Hannover and now is more often referred to as the "anterior knee" of Wilbrand (19). This anatomy helps to explain the two types of junctional scotomas seen with anterior chiasmal lesions.

Wilbrand and Saenger (18) noted that damage to
the anterior angle of the optic chiasm could result in an ipsilateral central scotoma with a contralateral upper temporal visual field defect that respects the vertical meridian. In 1920, Traquair (4) published the case of a 28-year-old woman who suffered from a large pituitary tumor. A monocular upper temporal scotoma occurred initially only in the right visual field (4). Later, in the classic text *Clinical Perimetry* (10) Traquair referred to this type of visual field defect again in a discussion of lesions of the optic nerve:

At the chiasmal termination of the nerve the diversion of the crossed from the uncrossed fibres permits of the predominant involvement of one of these groups, more especially as regards the macular fibres, and the production of unilateral hemianopic defects. Scotomata of this type may be called "junction scotomata" on account of their site of origin at the junction of the nerve and the chiasma. (10, p. 84)

Pathologic verification of the anatomy of temporal hemianopias in man was done by Unsold and Hoyt (20) who, at autopsy, obtained the left optic nerve of a patient with a blind right eye and a left temporal hemianopia due to an intracranial aneurysm. They showed that nasal segregation of the fibers destined to cross begins before the chiasm and commented that a lesion affecting the nasal side of one optic nerve could exclusively affect the temporal field of vision.

Unfortunately, the retinotopic organization of the afferent pupillary fibers is uncertain. The classical teaching is that the afferent limb of the direct pupillary light reflex (PLR) is subserved by axons
that partially cross at the optic chiasm and synapse in the pretectal area of the midbrain (21). In man approximately 47% of axons from retinal ganglion cells remain uncrossed, while 53% of fibers cross in the chiasm (22); this crossing asymmetry probably includes pupillary fibers and may partially explain contralateral relative afferent pupillary defects in optic tract hemianopias (23), and with lesions affecting the pretectal region as reported by Ellis (24). He described a right-sided pineal region tumor affecting only the pupillary pathways. Pupilllographically, the responses in the left eye were diminished and the patient had a clinically recognizable RAPD as a presenting sign. All other aspects of visual function were preserved, including visual acuity, visual evoked potentials, color vision, and visual fields. Similar cases have been reported subsequently (25,26).

Pierson and Carpenter (27) noted that, in monkey, the pretectal olivary nuclei (PON) receive more retinal projections than other pretectal nuclei and felt that they play the major role in the pupillary light reflex. In cat, Distler and Hoffman (28) noted bilateral, but predominantly crossed projections from eye to pretectal olivary nuclei with a ratio of crossed to ipsilateral of 17:6:1. Bilateral projections also occur to the pregeniculate nuclei (PGN), and the PGN in turn projects to the pretectal olivary nuclei. In primate retinal lesion studies, Polyak (Ref. 19, pp. 305–307; 335–335; 376–385) demonstrated that the majority of fibers projecting to the PGN came from the macular region of the retina, and he concluded that the PGN probably played an important role in the pupillary light reflex. Pierson and Carpenter (27) refuted this possibility by showing that lesions in PGN do not inhibit the light reflex in monkeys. They (27) suggested that PGN more likely plays a role in accommodation, since it receives inputs from cortical visual and visual association areas as well as from the retina. The pretectal olivary nuclei also receive direct cortical input from cat areas 17, 18,
FIG. 3. (A) Right visual field of patient 1 by Goldmann technique. (B) Left visual field of patient 1 by Goldmann technique.

19, and 20a (28). The lateral terminal nucleus of the accessory optic system may also play a role in the pupillary light reflex, since it is directly, but contralaterally, connected to the pretectal olivary nuclei (29).

Whether the fibers that are responsible for the pupillary light reflex are separate from visual fibers, or whether they are axon collaterals, has also been debated. Given that there are a group of retinal ganglion cells (W cells) that are luminance-sensitive and project to the pretectal region of cats (28,30–32), it is possible that separate axons are responsible for the pupillary light reflex. Centrally located W cells in the cat retina differ from the X retinal ganglion cells that most likely subserve visual acuity (33). However, Tychsen and Hoyt (34) found RAPDs contralateral to congenital occipital hemianopias in two patients. Both had homonymous hemiopic atrophy, presumably from transsynaptic degeneration. Their observations would be most consistent with a visual-pupillary axon collateral arrangement.

The evidence linking pupillary fibers to visual fibers is based upon the almost constant association of visual field loss with pupillary abnormalities. Furthermore, RAPDs most often occur in lesions, including amblyopia (35), that affect central vision, therefore implying that the bulk of fibers subserving the afferent arc of pupillary light reflex travel with, or are directly a part of, the papillo-
macular bundle. Yet, it is noteworthy that RAPDs occur in many patients with optic neuritis who regain normal central visual acuity (36-38). In the series of Kupersmith et al. (38) these cases recovered to 20/20 vision; contrast sensitivity functions were uniformly abnormal, thus raising the possibility that afferent pupillary information and contrast sensitivity information can be selectively damaged in optic neuritis. Wall (39) concluded that the functions of P retinal ganglion cells—comparable to cat X cells—are mainly affected in optic neuritis. Unfortunately, pupillary reactions were not measured in his study. Lastly, in a study correlating RAPDs with visual field defects detected by threshold static automated perimetry, Johnson and coworkers (40) described four patients with RAPDs but no detectable visual field defects. Conversely, certain lesions of the central vision, especially those caused by macular disease, do not present with RAPDs as a rule. In cat, the major projections to pretectal olivary nuclei are from ventral retinal ganglion cells (i.e., superior visual field) (28).

Thompson and coworkers (1) reported a linear relationship between the magnitude of the afferent pupillary defect and the amount of unilateral visual field loss measured by Goldmann perimetry; they found a more variable relationship between visual acuity and size of the RAPD. Furthermore, they did not specifically comment on temporal

FIG. 4. (A) Right visual field of patient 2 by Goldmann technique. (B) Left visual field of patient 2 by Goldmann technique.
hemianopias. Using their template technique on the kinetic visual fields of our patients, we calculated that all should have had clinically observable RAPDs (Table 2), although these were not noted by us. A similar correlation of visual field loss with the results of automated perimetry was reported by Johnson and coworkers (40), and their report strengthens the concept of pupillomotor representation concentrated within the central visual field.

Our observations also differ from the predictions indicated by the pupillographic phenomenon of contraction anisocoria observed in normal subjects (41, 42), wherein stimulation of nasal retina (i.e., temporal visual field) causes a greater direct and consensual reaction than does stimulation of temporal retina, thus suggesting a greater pupillomotor drive from nasal retina than temporal retina. The presence of an RAPD contralateral to an optic tract lesion is similarly explained by the predominance of crossed (i.e., nasal fibers; temporal visual field) versus uncrossed fibers in the optic tract (22), in accord with the well-known fact that temporal visual field is larger in area than is nasal visual field (23). It could be argued that, if we had used a more sensitive method like pupillography, our patients would have had RAPDs; if so, they clearly would have been of small magnitude. As noted above, Distler and Hoffman (28) found that cat ventral
Monocular temporal visual field loss

Retinal ganglion cells (i.e., upper visual field) are responsible for the majority of afferent input to the pretectal olivary nuclei. It is also possible that the use of a test light of lower intensity, as discussed by Borchert and Sadun (43), might have uncovered RAPDs in our cases. In any event, the ideal conditions for eliciting a RAPD are still under discussion (cf. refs 15 and 17 with 43).

The dissociation between monocular temporal visual field loss in our patients and absence of clinically detectable RAPD is open to a variety of interpretations. First, it is unlikely that errors in observation played a major role, since most patients were followed serially and examined by more than one ophthalmologist. Also, we have seen other patients with monocular temporal visual field defects who had RAPDs (Tomsak and Kosmorsky, unpublished).

Second, although monocular temporal defects are often considered a sign of nonorganic, or functional, disease, our patients differed in several respects. Two of our patients had tumors of the chiasmal region demonstrated by MRI or CT scanning, one had optic nerve damage from pseudotumor cerebri, one had carotid disease with a visible retinal embolus and presumed posterior ischemic optic neuropathy (PION), and one had sud-
den persistent loss of vision following head injury (traumatic optic neuropathy). Most visual field defects were reproducible over time.

One of our patients had visual field examinations by both Goldmann and Humphrey techniques (Case 1). No obvious differences were found, indicating that there was not an unrecognized subtle defect in the opposite eye or more generalized defects in the ipsilateral eye.

Why some patients with temporal hemianopias, as in our series, do not have RAPDs, whereas others do (7,8,11), implies that the visual pathways and pupillary pathways are functionally separate, and perhaps anatomically variable, especially in the region of the posterior optic nerve and anterior chiasm. In addition, our observations suggest that visual and pupillary pathways can be differentially affected by various types of lesions.

In closing, we wish to suggest that patients with monocular temporal visual field loss should not be

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**TABLE 2. Predicted relative afferent pupillary defects**

<table>
<thead>
<tr>
<th>Case</th>
<th>Predicted RAPD (log units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Calculations done by the method of Thompson et al. (1).
rejected out of hand as having a functional visual disturbance, even if a RAPD is not present. This visual field defect, which has exquisite localizing value to the ipsilateral and medial prechiasmal portion of the optic nerve, should prompt neuro-radiologic investigation. Furthermore, clearly more remains to be learned about the retinal distribution of ganglion cells involved in the afferent pupillary response to light.

Acknowledgment: The authors wish to thank Professor R. W. Guillery for his helpful comments.

REFERENCES

Suprasellar Tumors of Maldevelopmental Origin in Klinefelter's Syndrome
A Report of Two Cases

Latif M. Hamed, M.D., Bernard L. Maria, M.D., Ronald Quisling, M.D., Maher M. Fanous, M.D., and Parker Mickle, M.D.

Patients with Klinefelter's syndrome may have a predisposition for the development of neoplasia, particularly extragonadal germ-cell tumors, but a suprasellar location is rarely reported. The clinical and neuroradiologic features in two patients with Klinefelter's syndrome and dysmorphic suprasellar masses of maldevelopmental origin (presumably lipomas or lipodermoids) are described. One patient had bilateral optic atrophy and decreased vision. To our knowledge, only one similar case (a suprasellar hamartoma) has been previously reported in association with Klinefelter's syndrome.

Key Words: Klinefelter's syndrome—Suprasellar tumors.

Klinefelter's syndrome is a chromosomal abnormality characterized by 47XXY karyotype that is estimated to occur in 0.6% of live male births. Patients have sterility, testicular atrophy with hyalinization of the seminiferous tubules, gynecomastia, a eunuchoid habitus, and an increased level of follicle-stimulating hormone. Patients with Klinefelter's syndrome have an increased incidence of neoplasia, with breast carcinoma (1) and extragonadal germ-cell tumors (2) being most frequently described. The site of predilection for the extragonadal germ cell tumors is the mediastinum (3), but lesions involving the retroperitoneum and the central nervous system (4-7) have been reported. Other sporadic reports have described patients with Klinefelter's syndrome and lymphoma (7), leukemia (8), transitional cell carcinoma of bladder (9), prostatic carcinoma (10), adrenal carcinoma (11), bronchogenic carcinoma (12), reticulum cell sarcoma (13), and interstitial cell tumor of the testes (14).

Involvement of the central nervous system in patients with Klinefelter's syndrome is rare, with only three previously reported cases involving the hypothalamus or suprasellar region (15-17). We report two children with Klinefelter's syndrome and radiologically documented suprasellar masses.

CASE REPORTS

Case 1

A three-year-old boy was referred for evaluation of developmental delay and dysmorphic features.
He was a product of a full-term, uncomplicated pregnancy and normal vaginal delivery, weighing 6½ lb at birth. The umbilical cord was wrapped around the neck at delivery. He was initially cyanotic with poor Apgar scores, but the cyanosis resolved quickly after the umbilical cord was unwrapped.

There was a mild delay in achieving normal developmental milestones. Specifically, he showed a social smile at 6 months, began rolling over at 1 year, was able to sit at 12-14 months, stand and cruise at 1½ years, and babble at 15 months of age. There was no family history of developmental delay or genetic syndromes. Physical examination disclosed a hirsute child with microcephaly. His height of 82 cm, weight of 11.56 kg, and head circumference of 46.5 cm were all less than the 5th percentile for age. He had a low hairline, an abnormal right ear with a fold of the upper helix, and bilateral preauricular tags. The lungs and heart were normal. The liver edge was palpable 2-3 cm below the right costal margin. The testes were normal and descended. Neurologic evaluation showed generalized hypotonia with normal reflexes.

Eye examination disclosed central, steady, and maintained vision in both eyes with good fixation. Krimsky examination showed 30 prism diopeters of exotropia at near fixation. Cycloplegic retinoscopy showed high myopia in the range of -9.00 diopeters OU. Ocular pursuit was saccadic. There was no afferent pupillary defect. Fundus examination showed a prominent choroidal pattern with normal optic nerves, macula, and vessels. Visual evoked response showed low normal amplitudes, suggesting intact projections to the primary visual cortex.

The child had been previously diagnosed on the basis of clinical findings and chromosomal analysis as having Klinefelter's syndrome with a karyotype of 47XXY. Laboratory studies showed normal electrolytes, protein, albumin, and liver function tests.

Magnetic resonance imaging (MRI) of the brain revealed a large heterogeneous mass in the suprasellar space deforming the hypothalamus, the optic chiasm, the pituitary stalk, and causing obstructive hydrocephalus at the third ventricular (foramen of Monro) level (Fig. 1). The mass is largely cerebrospinal fluid (CSF) intensity but is not completely homogeneous. The inhomogeneity is related in part to pulsatile effects of CSF within a closed space creating flow related enhancement. This subtle hyperintensity is not reproduced in the same location on images in other planes. The anterior aspect of the mass contains a lipoid nodule located adjacent to the hypothalamus. The cystic part has no distinguishable capsule and does not arise from within the sella. These magnetic resonance findings are consistent with a combination of lipoma (or lipodermoid) and a cyst, either arachnoid or epidermoid. Other cystic lesions of the suprasellar space (Rathke's cyst or cystic craniopharyngioma) are less likely. Whether the nodular part of the lesion is a lipodermoid (cholesterol-containing) or whether it is a lipoma (mature adipose tissue) is difficult to distinguish by magnetic resonance. No soft tissue components were evident to suggest teratoma, hamartoma, or malignancy.

Case 2

A 5½-year-old white boy was referred for evaluation of a brain tumor. He is the product of a full-term pregnancy and breech extraction spontaneous delivery. He weighed 6.0 lb at birth. Gestation history was unremarkable. Developmentally, the patient was able to walk at 2 years of age, but was still unable to talk. He put puzzles together and stacked blocks. He understood well and listened to commands. The patient was admitted to a hospital for management of dehydration secondary to diarrhea. During the hospitalization, an EEG, computed tomography, and MRI of the head were performed to evaluate his developmental delay. The EEG was normal. Computed tomography and magnetic resonance studies revealed a shotty-type lesion with a fatlike consistency, 1 cm in size in the area of the tuber cinereum, most consistent with the diagnosis of intracranial lipoma or lipodermoid (Fig. 2). Chromosomal analysis showed a karyotype of 47XXY consistent with Klinefelter's syndrome.

Physical examination revealed a height of 113.5 cm (75th percentile), weight of 18 kg, and a head circumference of 51.5 cm. The nasal bridge was broad. Eye examination disclosed a visual acuity of 20/40 on the right and 20/80 on the left. The patient preferentially fixated with the left eye. He had 16 prism diopeters of right esotropia in primary gaze. The pupils showed no afferent pupillary defect. Dilated fundus examination revealed marked temporal pallor of the optic nerve heads, more on the right. The lungs, heart, and abdomen were normal. Neurological examination was normal. The testes were descended and of normal size. Thyroid panel and cortisol level were normal for age.
FIG. 1. Magnetic resonance sections illustrating the radiographic features of a large suprasellar mass characterized as two lipoid nodules and a large cyst of cerebrospinal fluid intensity. (A) Axial, T1-weighted, magnetic resonance image illustrating the deforming effects of this mass on brain structures forming the suprasellar space including the ventral mesencephalon (M) and the mesial left temporal lobe (T). The mass contains a nodule with lipoid intensity and an apparent cystic component with cerebrospinal fluid intensity. The rostral aspect of the cyst stretches the optic chiasm (Ch). The heterogeneous appearance of the cyst is likely related to cerebrospinal fluid pulsatility, since there is flow-related enhancement on the T1-weighted image, which is not reproduced in the coronal plate. However, it is possible that all or a portion of the cyst is actually an epidermoid cyst with near-cerebrospinal fluid intensity. Such lesions can be indistinguishable from arachnoid cysts. (B) Axial T2-weighted magnetic resonance image reveals heterogeneous signal from the cyst. Such heterogeneity is related in part to the lipoma (the low-intensity nodule, arrow) and in part to phase dispersion related to cerebrospinal fluid pulsatility during the scanning sequence. (C) Coronal, T1-weighted, Magnetic resonance section illustrates the stretched but otherwise normal pituitary stalk and a normal pituitary gland. The rostral aspect of the hypothalamic lipoma is also apparent (arrow). The cyst within the suprasellar space is cerebrospinal fluid density and causes no apparent displacement of the stretched but normally placed pituitary stalk and supraclinoid segments of the carotid arteries.

DISCUSSION

Miller (18) subdivides intracranial lesions of possible maldevelopmental origin into neoplastic, choristomatous, and hamartomatous categories. According to this subdivision, the neoplasms include germ-cell tumors, craniopharyngiomas (and the closely related Rathke's cleft cyst), and lipomas. Each of these tumors has a predilection for specific midline structures. For instance, the gonads, retroperitoneum, mediastinum, pineal gland, 3rd ventricle, and hypothalamus are the preferred sites for germ-cell tumors, while the corpus callosum, tuber cinereum, quadrigeminal

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plate, and ambient cisterns are the preferred sites for intracranial lipomas (18). In the absence of histopathological verification, the specific lesion may be pinpointed on the basis of clinical behavior, location, and neuroradiologic characteristics.

Other investigators argue against considering lipomas as neoplastic lesions (19). They provide clinical and neuroradiological evidence to support the concept that intracranial lipomas are best considered as congenital malformations, as opposed to neoplasms. Lipomas, according to this concept, arise as a result of abnormal differentiation of the primitive meninx, which normally gives rise to the subarachnoid space (19).
Chromosomal alteration appears to play a significant role in neoplastic disorders. Two of the relatively common trisomies, Down’s syndrome and Klinefelter’s syndrome, show a higher than normal risk for neoplasia. Patients with Down’s syndrome, for instance, show a propensity for the development of reticuloendothelial tumors (20). Patients with Klinefelter’s syndrome are at a greater risk for the development of breast cancer, germ cell tumors, and, to a lesser extent, other types of neoplasms (1-14). The reason for the higher incidence of neoplasia in Klinefelter’s syndrome is unknown, although hormonal changes and chromosomal abnormalities have been offered as explanations. It has been demonstrated that the XXY cells were transformed 3 to 10 times more frequently by the simian papovavirus 40 in patients with Klinefelter’s syndrome and tumors than in a normal control population (12).

Central nervous system neoplasms rarely occur in patients with Klinefelter’s syndrome. To date, only seven cases of Klinefelter’s syndrome with central nervous system tumors have been reported (4-7,15-17) (Table 1). Of the seven cases, five were pathologically proven germinoma (three affecting the pineal region, one affecting the posterior hypothalamus, and one affecting the suprasellar region). The sixth case is the first reported instance of a radiologically documented suprasellar hamartoma in Klinefelter’s syndrome (15). The seventh case is the first case with a pathologically proven primary B-cell lymphoma involving the right frontal and parietal lobes (7).

The magnetic resonance features of the first case appear to be those of a dysraphic mass partly lipoma but largely a nonencapsulated cyst. Ahagon et al. (16) described the computed tomography findings on a suprasellar germinoma with peripheral calcification and a low-density area, suggesting a cyst formation that led to the misdiagnosis of a craniopharyngioma preoperatively. In addition, our patient did not have any clinical evidence of diabetes insipidus. The magnetic resonance findings in Case 2 suggest fatlike material in the region of the tuber cinereum that most likely represents a lipoma. The tuber cinereum area is one of the preferred sites for intracranial lipomas (18).

Patient 2 presented with bilateral optic atrophy,

<table>
<thead>
<tr>
<th>Reference (no.)</th>
<th>Age (years)</th>
<th>Site of lesion</th>
<th>Histopathology</th>
<th>Neuroradiology</th>
<th>Ophthalmological findings</th>
<th>Systemic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubenstein (4)</td>
<td>16</td>
<td>Pineal gland</td>
<td>Germinoma</td>
<td>—</td>
<td>—</td>
<td>Enlarged blind spot, OD, inferotemporal visual field defect, OS</td>
</tr>
<tr>
<td>Chaussain et al. (15)</td>
<td>1</td>
<td>Hypothalamus</td>
<td>—</td>
<td>Circular mass in interpeduncular cistern, hamartoma of floor of third ventricle</td>
<td>—</td>
<td>Sexual precocity</td>
</tr>
<tr>
<td>Ahagon et al. (16)</td>
<td>20</td>
<td>Suprasellar area</td>
<td>Germinoma</td>
<td>Low-density area with peripheral calcification suggesting cyst formation</td>
<td>Enlarged blind spot, OD, inferotemporal visual field defect, OS</td>
<td>Polyuria, polydipsia</td>
</tr>
<tr>
<td>Ellis et al. (17)</td>
<td>12</td>
<td>Posterior hypothalamus</td>
<td>Germinoma</td>
<td>Irregular mass of mixed attenuation arising from midline</td>
<td>Bilateral papilledema, skeletal deformities</td>
<td>Scoliosis, skeletal deformities</td>
</tr>
<tr>
<td>Arens et al. (5)</td>
<td>15</td>
<td>Pineal gland</td>
<td>Germinoma</td>
<td>Ill-defined 3-cm density dorsal and inferior to pineal gland</td>
<td>Dorsal midbrain syndrome</td>
<td>Grand mal seizures</td>
</tr>
<tr>
<td>Oki et al. (6)</td>
<td>17</td>
<td>Pineal gland</td>
<td>Germinoma</td>
<td>Tumor shadow around calcified pineal extending to suprasellar region Hypodense lesion at right frontoparietal area</td>
<td>—</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Liang et al. (7)</td>
<td>33</td>
<td>Frontal and parietal lobes</td>
<td>B-cell lymphoma</td>
<td>—</td>
<td>—</td>
<td>Left hemiparesis, HIV-negative</td>
</tr>
<tr>
<td>Present Case 1</td>
<td>3</td>
<td>Suprasellar area</td>
<td>—</td>
<td>Large cystic mass in suprasellar cistern</td>
<td>—</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>Present Case 2</td>
<td>5½</td>
<td>Suprasellar area</td>
<td>—</td>
<td>1 cm fatlike mass</td>
<td>Bilateral optic atrophy OD &gt; OS</td>
<td>Developmental delay</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus
more marked on the right. Patients with Klinefelter’s syndrome and optic atrophy may need to undergo neuroimaging of the head to rule out a perichiasmal mass lesion. Alternatively, it is possible that some patients with similar suprasellar lesions have undiagnosed Klinefelter’s syndrome, as the diagnosis may be missed if chromosomal analysis is not performed. This is particularly relevant, since an associated hypogonadism in a patient with a suprasellar lesion may be attributed to secondary disruption of the pituitary-hypothalamic axis rather than to an underlying Klinefelter’s syndrome (in which hypogonadism is a characteristic feature). The two disorders may therefore be confused with one another clinically.

In a prospective study of 22 patients presenting with mediastinal germ-cell tumor, Nichols and associates (3) found five of them to have previously unsuspected Klinefelter’s syndrome upon chromosomal analysis. A similar study addressing the prevalence of Klinefelter’s syndrome in patients with intracranial germinoma may be useful.

REFERENCES

Permanent Homonymous Hemianopias Following Migraine

Masato Wakakura, M.D., D.Sc. and Yoshiaki Ichibe, M.D.

Two patients with migraine and repetitive visual field defects of homonymous hemianopic type are reported. The visual field defects were confirmed by Goldmann perimetry and automated static perimetry. Neither computed tomography nor magnetic resonance imaging showed abnormal findings. Decreased cerebral blood flow at the left basal ganglion area was the only abnormal finding detected in one patient by \(^{123}\text{I-IMP (iodoamphetamine)-SPECT (single photon emission computed tomography)}}\), which is applicable to right homonymous hemianopia. A visual field test that includes the current automated static perimetry is important to the diagnosis and the subsequent treatment of patients with migraine, particularly those who have experienced visual negative phenomena.

Key Words: Hemianopia-Migraine-Visual negative phenomenon-Automated static perimetry-Single photon emission computed tomography.

Migraine usually affects relatively young people and often occurs without abnormalities detectable by neuro-ophthalmologic examinations. However, there is evidence that a benign clinical course (1) is not followed in all cases. Several cases of migraine ischemic optic neuropathy have been reported (2-6). A young, otherwise healthy, woman with migraine was found to have bilateral disk edema and retinal hemorrhage (7). Kupersmith et al. (8) reviewed 46 complicated migraine patients with visual dysfunction. Lewis et al. (9) noted visual field abnormality at a surprisingly high frequency (35%) in 60 migraine patients while conducting automated static perimetry. Three of the subjects had homonymous hemianopia. In this study there were two patients with migraine accompanied by repetitive visual negative phenomena of the homonymous hemianopic type. They eventually had permanent retrochiasmal visual field defects. Although migraine cases with permanent visual field loss due to probable or definite retrochiasmal lesion have been mentioned in the older literature (10-12), two similar patients examined by current automated static perimetry and single photon emission computed tomography (SPECT) are here reported.

CASE REPORTS

Case 1

The subject was a 24-year-old man with increasingly frequent throbbing headaches affecting particularly the right temporal portion, of about 2 months duration. Headaches had recently occurred every day for several hours duration and were sometimes accompanied by nausea and/or vomiting. One month before, he noted a right visual field defect on awakening. He consulted a private neurosurgeon who found no abnormality by brain computed tomography (CT). No hyperten-
sion was noted. The visual field defect varied considerably in size from day to day, and complete recovery was never attained.

The neurosurgeon referred the patient to Kitasato University Hospital in September 1989. Visual acuity was 20/20 OU, and Goldmann perimetry showed incongruous right homonymous hemianopia with macular sparing. Plain and enhanced brain CT showed no abnormal findings. Spin echo magnetic resonance imaging (MRI) by 0.5 tesla indicated no abnormal findings on T1-weighted or T2-weighted images with tomographic slices of 10 mm in width. No gadolinium enhancement was performed. Without treatment, the field appeared to have recovered in mid-October. Goldmann perimetry showed significant improvement in the visual field of each eye, but the right field defect was shown to persist by both the 30-2 threshold program of the Humphrey Visual Field Analyzer and conventional Goldmann perimetry.

At the end of October, examinations were conducted at the Department of Medicine because of sinus tachycardia and arrhythmia, which had developed suddenly at midnight. The symptoms were transient and the cause unknown. Echocardiography indicated normokinesis.

Several days later, severe throbbing headache occurred again, and the patient went to bed. On the following morning, he noted the right visual field defect of each eye to have enlarged. He was subsequently hospitalized at our department. Blood tests showed mild liver dysfunction (glutamic-oxaloacetic transaminase 30 IU/L, glutamic-pyruvic transaminase 54 IU/L), mild hyperlipidemia (cholesterol 247 mg/dl, triglyceride 264 mg/dl), and RA (+). The results of an erythrocyte sedimentation test (10 mm/h), negative C-reactive protein and negative antinuclear antigen failed to give any indication of vasculitis. The maximum platelet aggregation rate examined by 2.25 µM adenosine diphosphate showed 58%, this being slightly high (normal 30-55%). SPECT, using a tracer, N-isopropyl-p-[123I]iodoamphetamine (IMP), was conducted, following essentially the same method described by Schlake et al. (13).

In brief, 20 minutes following an intravenous administration of 123I-IMP, 64 early scan images were obtained with a rotation gamma camera (General Electric MaxiCamera 400ACT). The imaging time per image was 40 seconds, and each examination took 35 minutes. Late scan was also done 4 hours after the tracer administration. The early scan facilitated the assessment of regional cerebral blood flow (rCBF) (14) and indicated decreased CBF in the left basal ganglion area (Fig. 1). CBF in the bilateral occipital portions, however, appeared normal or to have slightly increased.

The patient was given aspirin (250 mg/day) and Inderal (2 tablets/day). Severity of the headaches subsequently abated somewhat. However, the vi-

FIG. 1. Early scan image of [123I]iodoamphetamine single photon emission computed tomography in Case 1. (A): Transverse and (B) coronal sections. Arrows indicate decreased tracer uptake by left basal ganglion area.
sual field defect again fluctuated, and, finally, a condition of permanent right homonymous hemianopia developed.

Neither MRI nor SPECT in March 1990, at the time the headaches ceased, showed abnormal findings except for possibly increased CBF in both occipital areas, according to SPECT. Dynamic CT in June showed no abnormality. The time course of the visual field is shown in Fig. 2.

Case 2

The subject was a 39-year-old woman who had had occasionally throbbing headaches of the frontal or temporal portion for approximately 10 years duration. The family history was negative for migraine headaches. She had no hypertension. At the end of October 1987, she felt deep right orbital pain and transient visual loss in both eyes. The symptoms were relatively quickly relieved, but a right visual field defect was noted. She consulted an ophthalmologist. Right homonymous hemianopia was detected by an automated static perimeter.

Goldmann perimetry conducted 2 days later showed slight depression of the right visual field of each eye.

The patient was referred to the Department of Ophthalmology, Kitasato University Hospital on November 9, 1987. At that time, the patient felt she had the complete recovery of the visual field of each eye. Goldmann perimetry showed normal findings as did also brain CT. The patient had no visual symptoms afterward, although, on some occasions, there were headaches.

On September 30, 1989, the patient had a strong throbbing left temporal headache for several hours. Two days later, the headache disappeared, but darkness of the right half-field was noted. Visual acuity was 20/20 OU. The 30-2 threshold program of Humphrey Field Analyzer showed decreased sensitivity of the right lower field in each eye. Blood tests that indicated determination of the erythrocyte sedimentation rate, platelet aggregation, titer of antinuclear antigen and immunoglobulins showed no abnormality. MRI indicated normal findings. $^{123}$I-IMP-SPECT showed no defi-
nately abnormal findings, but there was indication of what appeared to be slightly increased bilateral occipital CBF.

The visual field showed right homonymous hemianopia with macular sparing on September 28, 1989. The time course of each field is shown in Fig. 3. During follow-up for 1 year, the fields significantly improved, but permanently decreased sensitivity persisted in the right peripheral field of each eye.

DISCUSSION

Homonymous hemianopic visual field defects in the patients discussed here indicated retrochiasmal lesions. At least 13 patients with migraine, along with probable or definite retrochiasmal visual field defects, have been reported (8,10–12). Two relatively old patients (a 60-year-old woman and a 54-year-old woman) of Hollenhorst (11) and one patient (a 47-year-old man) of Connor (12) appeared to have late-onset migraine headaches. These may have been secondary to age-related vascular disease of the brain. The remaining 10 reported patients, as well as our 2 patients, are quite likely typical cases in which, etiologically, there is a direct relationship between migraine headaches in young patients and retrochiasmal lesions.

Unlike the previously reported cases, our two cases are characterized by initially transient but ultimately permanent visual field defects. The reason why the visual fields fluctuated over months to years is unknown, since no lesion could be found by computed tomography, magnetic resonance imaging, or dynamic computed tomography. Decreased cerebral blood flow in the left basal ganglion area detected by single photon emission

FIG. 3. Clinical time course of visual field defect in Case 2.
computed tomography in Case 1 was the only objective finding, indicating possibly decreased flow of the left posterior cerebral artery or its branches. Although this is not direct evidence for left occipital hypocirculation, decreased flow of the left posterior cerebral artery is consistent with the right homonymous hemianopia noted in this patient. Prolonged, relatively mild, hypoperfusion to the responsible area may have caused fluctuation of visual field defects and pathologic changes undetectable by presently available means.

The permanent visual field defects may have been due to intolerance of prolonged hypoperfusion. Occipital lobe arteriovenous malformations (10,15) should also be considered for differential diagnosis in our two cases. However, in addition to CT and MRI, dynamic CT, shown to be useful for detecting cerebral vascular anomalies (16), failed to indicate any abnormality in the occipital area. SPECT showed somewhat slightly increased CBF in the bilateral occipital areas, but these findings are not an actual indication of the presence of occipital lobe arteriovenous malformations. Brain angiography was not performed for the following reasons: other neurological symptoms were absent, there was continued good visual acuity, and there was insufficient indication for surgery.

There was no scintillating scotoma (visual positive phenomenon) preceding temporally visual negative phenomenon or visual field loss in our cases. In only one case of Symonds (10), did scintillating scotoma appear to have continued after visual field loss. Similar continuity has been noted in a case with metastatic melanoma (17). A temporally visual negative phenomenon was demonstrated in 8 of the 10 reported (8,10-12) patients and our 2 patients. The visual negative phenomenon may thus be more important as a warning sign for organic disease. Current automated static perimetry facilitated the detection of transient and permanent visual field defects, as also noted by Lewis et al. (9). Study of the central field has also been found clinically useful for patients showing visual negative phenomena, even after subjective symptoms have subsided and in the absence of objective findings (CT, MRI, SPECT).

In conclusion, since migraine headaches do not always follow a benign clinical course, examination should be made of the static visual field, particularly for patients with such headaches and visual negative phenomena.

Acknowledgment: Dr. Toshimasa Fukuda is gratefully acknowledged for having referred Case 2 to our department.

REFERENCES

Transient Oculomotor Nerve Synkinesis in Non-Hodgkin’s Lymphoma


A patient with large cell malignant lymphoma presented with transient left oculomotor nerve synkinesis, left trigeminal and abducens nerve palsies. Magnetic resonance imaging showed thickening of the oculomotor and trigeminal nerves characteristic of central nervous system lymphoma. To our knowledge, this is the first reported case of transient oculomotor nerve synkinesis in non-Hodgkin's lymphoma. The rapid onset and quick recovery of the synkinesis following 2 weeks of chemotherapy support the ephatic transmission theory.

Key Words: Lymphoma—Transient oculomotor nerve synkinesis—Ephatic transmission—Magnetic resonance imaging.

CASE REPORT

A 44-year-old Chinese lady was admitted with a 1-month history of giddiness, left facial numbness, and frequent generalized headache. Three days prior to admission she had fever with chills and rigors as well as diplopia on looking downward. There was no diplopia on looking sideways. There was no facial asymmetry, hearing impairment, weakness, or numbness of the limbs. She did not have joint pain or loss of appetite or weight. There was no history of hypertension, diabetes mellitus, or other significant medical conditions.

Clinical examination revealed a well-nourished lady who was febrile with a temperature of 38°C. The blood pressure was 130/80 mmHg and pulse rate was 90/min. She was conscious and rational. The neck was supple. The right pupil was 2 mm in diameter and reactive to light, whereas the left pupil measured 4 mm and reacted sluggishly. There was partial ptosis and impairment of elevation, depression, and adduction of the left eye. Visual acuity was normal. There was hypoesthesia over the area supplied by the maxillary and mandibular branches of the left trigeminal nerve. The left corneal reflex was present. There were no cerebellar or long tract signs. Examination of the heart, lungs, and abdomen revealed no abnormalities and there was no significant lymphadenopathy.
She continued to have a remittent fever while in the ward. Two weeks after admission she developed partial left abducens nerve palsy, and paradoxical retraction of the left upper eyelid on downward gaze (Fig. 1). There was no pupillary synkinesis associated with ocular motility. The left trochlear nerve function was intact.

The hemogram showed pancytopenia (hemoglobin: 10.7 g/dl, white blood cells: 2,100/μl, and platelets: 20,000/μl). Bone marrow biopsy showed large cell malignant lymphoma. Cerebrospinal fluid (CSF) examination was normal, but cytospins of the CSF were not done. Septic workup and immune markers were negative. Chest x-ray was normal. Magnetic resonance imaging (MRI) showed a mass over the medial aspect of the left temporal lobe abutting on the cavernous sinus and thickening of the left trigeminal (Fig. 2) and oculomotor nerves (Fig. 3). All the lesions enhanced well with gadolinium.

Chemotherapy was started about 4 weeks after admission using the MACOP-B regimen (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone, and bleomycin). The fever subsided rapidly after the first dose of chemotherapy. Two weeks after treatment, all extraocular movements recovered without any trace of synkinesis (Fig. 4). However, the left pupil, though reactive to light, was still larger than the right.

In summary, this patient had non-Hodgkin's lymphoma and possibly central nervous system involvement as evidenced by the dramatic response of the neurological deficits to chemotherapy.

**DISCUSSION**

Lymphoma can affect the nervous system in several ways. Extradural spinal cord compression, cranial bony and dural involvement, cranial and peripheral nerve infiltration (5), infiltration of brain parenchyma (6) and leptomeninges (7) have been reported. The overall incidence of central nervous system (CNS) involvement in lymphoma is around 10% (8–10). The pathogenesis is unknown.
OCULOMOTOR NERVE SYNKINESIS

FIG. 3. Gadolinium magnetic resonance imaging (TR = 700 msec, TE = 12 msec) showing thickened left oculomotor nerve (arrow).

The commonest presentation of CNS lymphoma is cranial nerve palsies. The facial nerve is most commonly involved. Occasionally two or more nerves may be involved (7,8). Despite the predilection for cranial nerves, this is the first reported case of transient oculomotor nerve synkinesis in non-Hodgkin's lymphoma. These paradoxical movements are usually seen at least 6 weeks after acute third nerve paralyses caused by trauma, intracranial tumors, intracranial aneurysms, syphilis, or septic cavernous thrombosis (11,12). Three mechanisms have been postulated for these paradoxical movements, namely, aberrant regeneration (13), ephatic transmission (14,15) and chromatolysis-induced reorganization of nuclear synapses (14,16). Our case is unique in that the synkinetic movement appeared about 2 1/2 weeks after the acute 3rd cranial nerve injury and disappeared 2 weeks after starting chemotherapy. The rapid onset of the synkinesis and its transient nature would strongly support the ephatic transmission theory. This is an electrotonic, as opposed to chemical, spread of impulses between cells (15). The ephapse between adjacent cells could have been created by demyelination (17), which is not uncommon in CNS lymphoma. In aberrant regeneration there is misdirection of regenerated axons so that they innervate muscles to which they do not belong (13). Misdirection is not the likely cause in our patient because a much longer time than 6 weeks would be needed for regression of misdirected axons followed by regrowth of properly oriented oculomotor nerve axons (14).

In conclusion, this is the first reported case of transient oculomotor nerve synkinesis in non-

FIG. 4. Complete recovery of ptosis, extraocular movements and synkinesis following 2 weeks' of chemotherapy.
Hodgkin's lymphoma. It illustrates the fact that the MRI scan can aid in the diagnosis of CNS lymphoma by demonstrating cranial nerves thickening. The transient synkinesis supports the ephatic transmission theory.

REFERENCES

Myxoma Mix-Up
A Case Report


We present a 63-year-old lady who had atrial myxoma. The diagnostic difficulties distinguishing this from giant cell arteritis are highlighted. In particular, both conditions cause choroidal and retinal infarcts, anterior ischaemic optic neuropathy, with raised acute phase reactants. The authors stress the importance of continued ophthalmoscopy as the fundal changes become more apparent.

Key Words: Atrial myxoma—Giant cell arteritis—Diagnosis.

Atrial myxoma can present in one or a combination of three ways: (a) obstruction to cardiac flow, (b) embolic phenomena, 50% of which are to the brain, and (c) systemic symptoms and signs, including fatigue, fever, weight loss, and skin rashes (1). Investigations may show an elevated erythrocyte sedimentation rate, elevated serum globulins, and reduced serum complement levels.

We report a case of atrial myxoma, which was initially mistaken for giant cell arteritis.

CASE REPORT

A 63-year-old lady collapsed after swimming. On presentation she was unconscious, had a right-sided hemiplegia, and had facial palsy. Both plantar responses were extensor. The left pupil reaction was reduced and the optic disk on this side was pale. No cardiovascular abnormality was detected.

Her only previous medical history was migraine for which she received Migril.

The following investigations were normal: full blood count, biochemical profile, 12-lead electrocardiogram, and chest radiograph. The erythrocyte sedimentation rate was 53 mm/h.

On recovery to consciousness 5 days later, she reported reduced vision in the left eye. She also reported a headache which had predated the collapse by 1 week. This was associated with a 2-week history of malaise and fatigue.

On examination the acuity of the right eye was 20/20. This eye was normal in all respects. The left eye perceived light only and had an afferent pupillary defect. The left optic disk was pale and swollen, and there was loss of retinal transparency most marked in the macular area and in a wedge-shaped area nasal to the optic disk. The fundus picture was consistent with anterior ischaemic op-
tic neuropathy and short ciliary and central retinal artery occlusion. Cranial computerized tomography identified an infarct in the internal capsule.

A temporal artery biopsy showed luminal narrowing due to intimal fibroelastic proliferation of the lumen. There was no inflammatory cell infiltrate and no giant cells were seen.

A tentative diagnosis of giant cell arteritis was made and oral prednisolone, 60 mg/day was commenced. The headache improved, but the vision in the left eye remained severely reduced.

Six months following initial presentation she suffered a 10-minute episode of loss of vision in her right eye. This was described as a sea of black filling up from the bottom of her vision. Examination of the eye failed to reveal any abnormality. The erythrocyte sedimentation rate was now 32 mm/h.

Following this episode, an echocardiogram was undertaken, revealing an atrial myxoma, which was successfully resected 1 week later. Following this procedure, steroid therapy was tailed off. The erythrocyte sedimentation rate has remained low.

At routine follow-up, 2 months after surgery,

**FIG. 1.** Fundus photographs of the left eye at presentation (above), showing a pale swollen optic disk, retinal vascular occlusion and an area of choroidal infarct nasal to the disk. Four months later (below), the choroidal infarct demonstrates a wedge-shaped zone of pigment epithelial atrophy and hyperpigmentation.
ophthalmoscopy of the affected was markedly different. There was evidence of central retinal artery occlusion, with retinal arterioles occluded and several choroidal infarcts (choroidal pigmentation seen in the fundus photograph), in addition to anterior ischaemic optic neuropathy.

DISCUSSION

Duke Elder (2) reminds us that the infrequency of central retinal artery emboli from cardiac sources is due to two right-angle bends, one as the artery leaves the carotid, and the other as the central retinal artery leaves the ophthalmic artery. Ophthalmic complications of atrial myxoma are rare, with 11 reported cases of central retinal artery occlusion. Choroidal infarcts were also noted in two of these cases (3), indicating the presence of multiple emboli, characteristic of myxoma.

Our patient exhibited the three major diagnostic features for giant cell arteritis (age greater than 55, positive response to steroid within 48 hours, history longer than 2 weeks) and, in the absence of a positive temporal artery biopsy, three of the minor features (systemic symptoms) as classified by Ellis and Ralston (4).

The occurrence of central retinal artery occlusion, ischaemic optic neuropathy, and choroidal infarct in the same eye is especially suspicious of atrial myxoma, but has also been seen in giant cell arteritis (3).

There is considerable symptomatic overlap between atrial myxoma and giant cell arteritis. Both cause malaise and fatigue and a high erythrocyte sedimentation rate. Both cause neurological disorders by their effect on the vascular system with few specific clinical signs. Both can cause visual loss.

This patient caused considerable diagnostic confusion, her age being at the upper end of one condition and the lower end of the other. Ophthalmoscopic examination is important. Atrial myxoma usually causes a central retinal artery occlusion, giant cell arteritis anterior ischaemic optic neuropathy. The importance of continued ophthalmoscopy is stressed as possible coexisting choroidal infarcts become more prominent.

Acknowledgments: We are grateful to Professor A. R. Fielder and Dr. R. A. Stockley for their advice and for allowing us to report this case.

REFERENCES

Myasthenia Gravis-like Syndrome Induced by Topical Ophthalmic Preparations
A Case Report


This case study reports on a 64-year-old female who presented for cataract surgery. She relayed a history of allergic responses to local anesthetics such as xylocaine, but was otherwise in good health. Upon instilling ophthalmic preparations into her eyes during routine ocular examination, she developed general muscular weakness but not other allergic-like symptoms. Further investigation established her myasthenic-like syndrome to be precipitated by an ophthalmic mydriatic preparation. She was able to undergo uneventful cataract surgery and enjoy 20/20 vision postoperatively, with proper management.

Key Words: Tropicamide—Cataract surgery—Ophthalmic preparation—Myasthenia gravis.

A 64-year-old registered nurse was referred to our clinic by her family physician for evaluation of her cataracts. Her ophthalmic history noted only her decreased vision due to the cataracts, and dry eyes. Family history was insignificant except that she remembered that her late mother never underwent any local anesthesia.

The patient wore a medic alert bracelet indicating an allergy to Xylocaine. She reported an episode 20 years ago in a dentist’s chair when, after receiving a local anesthetic, she experienced a reaction that was interpreted as allergic in nature and she was advised never to have local anesthesia again. She clearly remembers the difficulty she had talking, as well as her shoes falling off her feet. Her recovery at that time was uneventful. She also recalled receiving a general anesthetic 20 years ago for a minor procedure, from which she took a long time to recover. Her general health was now good, however, and she was on no medications.

As part of her routine ophthalmic examination the following eyedrops were instilled about 5 minutes apart: tropicamide 1%, phenylephrine HCl 2.5%, and proparacaine HCl 0.5%. Ten minutes later, she stated that she felt as if she were “floating.” She was not dizzy or nauseous, but felt “high.” The physical examination revealed the following findings: flushed face, sweaty hands, dry mouth, clear lungs, no laryngospasm, normal heart sounds, blood pressure of 180/95 mm Hg, and a pulse rate of 60/minute (sinus rhythm). She was fully aware and conscious, but lethargic. It was decided to only observe the patient and not to take any active intervention. After 1 hour she was feeling well again, and her vital signs were normal, with a blood pressure of 124/84 mm Hg.

The clinical picture that we observed did not fit in with a typical allergic reaction. The absence of signs of histamine release, such as urticaria,
chemosis, laryngospasm, bronchospasm, and hypotension, led us to doubt the previous diagnosis of an allergy to local anesthetics. The presence of dry mouth, flushed face, bradycardia, and hypertension was suggestive of an anticholinergic response. Her lethargy, slurred speech, and muscle weakness prompted us to convince the patient to consent to our rechallenging her with the same medications but administered separately. She consented, and the test was performed about 2 weeks later.

Baseline observations included blood pressure; pulse; electrocardiogram; body temperature; upper extremity motor power for grip, flexion and extension; lower extremity motor power for flexion and extension; speech; ptosis; and diplopia. A venous access was established before instillation of any drops.

One drop of tropicamide 1.0% was instilled first. Within 3 to 4 minutes after instillation she responded, subjectively and objectively, in exactly the same manner as before. Her motor power in both upper and lower extremities was 3/5 compared with 5/5 before the reaction. She was slightly tachypneic, but not markedly distressed. She had developed a ptosis in both upper lids, spoke slurring, felt “high,” experienced no diplopia, was fully aware and conscious, but utterly lethargic. An intravenous injection of 1.5 mg edrophonium chloride dramatically reversed the reaction within a matter of seconds. Her muscle power was restored (5/5), speech had returned to normal, the ptosis had disappeared, and she had no more subjective feelings of general weakness.

After a half-hour she remained fine, and paroparcaine drops 0.5% were instilled, one drop in both inferior fornices. Within 2 minutes she experienced exactly the same reaction as before. Once again, it was fully reversed with 1.5 mg edrophonium chloride.

The last drug to be tested was phenylephrine 2.5%. She experienced absolutely no adverse responses to this drug in drop form. Qualitative acetylcholine receptor antibodies were tested for, but were absent, and the clinical diagnosis of drug-induced myasthenia-like syndrome was established.

Cataract surgery was subsequently successfully performed under local anesthesia. The patient once again developed the same syndrome of general muscular weakness after both the topical drops and the retrobulbar anesthetic. Her vital capacity was monitored throughout with a Wright’s respirometer, and it too was severely reduced from 2.8 L at baseline to 0.5 L after the retrobulbar block. Intravenous edrophonium chloride reversed both the muscular weakness and the respiratory depression dramatically. Edrophonium chloride, a well-known short-acting drug, was needed in a 2 mg intravenous dose at four intervals throughout the entire procedure. Surgery was uneventful, and the patient enjoys 20/20 vision postoperatively.

DISCUSSION

It has been well documented that myasthenia-like syndromes can be induced by a vast number of drugs (1-14). Numerous pharmacologic agents, such as neuromuscular blockers, antibiotics, anticholinesterase agents, antiarrhythmics, anti-inflammatory agents, beta blockers, corticosteroids, D-penicillamine, chloroquine, lithium, and magnesium, can also decrease transmission at the neuromuscular junction. Even toxins released by certain species of scorpions, ticks, wasps, spiders, and bacteria can also act at the neuromuscular junction.

The pathogenesis of drug-induced myasthenia gravis-like syndrome (DMG) is not clear. Current theories on the mechanism of DMG focus on altered immunological reactivity. A population of B-cell lymphocytes has apparently been induced to manufacture antibodies to the acetylcholine receptors (10). This action could be the result of several mechanisms: (a) altered acetylcholine-receptor antigenic properties, which make self-recognition more difficult (15); (b) a loss of suppressor T-cell control over B-cell production of antibodies—in vitro studies demonstrate that D-penicillamine decreases T-cell division (16); (c) direct stimulation of B cells, specific or nonspecific, which would lead to increased levels of antibodies (10); and (d) a direct toxic effect of the drug on the acetylcholine receptor (17). It is a very rare occurrence, however, to have this syndrome precipitated by a topical ophthalmic preparation. Coppeto (3) reported a case of DMG after use of topical timolol 0.5% twice a day for 2 months. An increased acetylcholine-receptor antibody level of 4.0 nmole (normal range, 0.0 to 1.0 nmole) was found. With discontinuation of the eyedrops the symptoms disappeared.

We were unable to find any reports in the literature of proven myasthenic-like syndromes precipitated by any of the ophthalmic preparations used in our patient. The rapidity of onset of the systemic reactions has once again highlighted the well-known pharmacologic principle that absorption of drugs transconjunctivally occurs directly into the conjunctival capillaries or via the nasal mucosa. As a result, the metabolic conjugation
pathways within the intestinal mucosa and the first-pass liver effects are eliminated (18). Consequently, a medication placed in the eye may exert a greater pharmacologic (or immunosensitizing) effect than one administered orally. So often, this fact is not fully appreciated by medical staff administering topical preparations to patients.

Therefore, we must recognize that potential inadvertent reactions to ophthalmic preparations are a reality and that these drugs should always be used and prescribed by medical staff who are well versed in pharmacology and the side effects of drugs. An eyedrop is as much a medicinal drug as an ampoule used for parenteral injections and should be used with the same amount of caution and respect.

REFERENCES

Literature Abstracts


The authors describe an 86-year-old man with a 35-year history of smoking who presented with visual loss. Computed tomographic scanning of brain and orbits was normal. Electroretinography became flat within several months, and 1 month following his visual loss small cell carcinoma of the lung was diagnosed. Serum antibodies to the retina were detected but were not greatly elevated initially. Several months later, serum antibodies were found to be more elevated in association with clinical worsening of visual function; thus prednisone therapy was begun. Subsequent antibody determination showed a decline. The authors argue that antibody determination in this patient helped guide therapeutic intervention.

*Lyn A. Sedwick, M.D.*


In the first article, the authors studied 78 patients (156 eyes) with acquired immunodeficiency syndrome (AIDS) and found defects of color vision and contrast sensitivity even without florid retinopathy. They postulate that a primary optic neuropathy may occur with AIDS or with a human immunodeficiency virus (HIV)-related process. The second paper describes optic nerve axonal loss at autopsy of AIDS patients, which supports the hypothesis of a primary optic neuropathy with AIDS.

*Lyn A. Sedwick, M.D.*


Sixteen patients, 26 eyes, with optic nerve drusen were subjected to pattern visual evoked potential and pattern electroretinography. Their results suggest that abnormalities can be detected in these tests even without significant visual loss with optic nerve drusen.

*Lyn A. Sedwick, M.D.*


Two patients with multiple sclerosis developed periphlebitis and retinal ischemia. One had initial mild uveitis and the other subsequently developed a granulomatous uveitis. Extensive testing for
other causes of uveitis and retinal neovascularization was unrevealing.

Lyn A. Sedwick, M.D.


A 35-year-old nonalbino man with horizontal congenital nystagmus had visual evoked potential testing with full and hemifield stimulation with checkerboard pattern. He was found to have probable nondecussation of nasal retinogeniculate fibers in the chiasm. Ocular motility was studied and suggested an association between the nondecussation and reversed visual tracking and congenital nystagmus.

Lyn A. Sedwick, M.D.

Hypertropia After Implantation of a Molteno Drainage Device. Munoz M, Parrish R. *Am J Ophthalmol* 1992;113:98–100 (Jan). [Inquired to Dr. M. Munoz, Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.]

Following implantation of a Molteno tube in the superotemporal quadrant left eye, this patient developed a worsening left hypertropia, which the authors felt arose from a fat adherence syndrome.

Lyn A. Sedwick, M.D.


A diabetic patient with an ischemic oculopathy but no ipsilateral retinopathy (by clinical examination or intravenous fluorescein angiography) underwent carotid endarterectomy. Six weeks later, he developed retinopathy and macular edema in the eye, raising again the question of a “protective” effect of significant carotid occlusive disease to the development of diabetic retinopathy.

Lyn A. Sedwick, M.D.


Two patients with central retinal artery occlusion and temporal arteritis had near complete return of vision following therapy with intravenous methylprednisolone. One had fluctuating visual loss even prior to treatment, but the other had no light perception for 24 hours pretreatment. These truly amazing cases are discussed in detail.

Lyn A. Sedwick, M.D.

Diagnostic Value and Limitations of Orbital Biopsy in Wegener's Granulomatosis. Kalina PH, Lie JT, Campbell RJ, Garrity JA. *Ophthalmology* 1992;99:120–4 (Jan). [Reprint requests to Dr. J. T. Lie, Department of Pathology, Mayo Clinic/Hilton 11, 200 First St., S.W., Rochester, MN 55905.]

Mayo Clinic patients from 1976 to 1991 identified from a computer search as having a diagnosis of Wegener's granulomatosis form the study group. All patients (14) with orbital biopsy were reviewed and those with tissue available for study (13) form the cases of this report. The findings on biopsy were variable with granulomatous inflammation present in 62% but multinucleated giant cells in only 31%. Small-vessel vasculitis was seen in 85%. The authors stress the importance of correlating these biopsy findings with extrabital findings and serological testing (antineutrophil cytoplasmic antibody) in order to confirm this diagnosis.

Lyn A. Sedwick, M.D.

The authors used color Doppler imaging to demonstrate concomitant decreased flow through the central retinal artery in a patient with an intracranal mass and gaze-induced amaurosis. These findings disappeared following removal of the orbital varix.

Lyn A. Sedwick, M.D.


Records of 54 patients with the diagnosis of Leber's congenital amaurosis were reviewed from a 15-year period at Johns Hopkins Center for Hereditary Eye Disease. Thirty-five met strict criteria for Leber's. Most patients showed retinal changes only with the passage of time often with normal initial examination, especially if done before age 1. Older patients in whom visual function could be adequately assessed did not have ongoing visual loss even when retinopathy worsened.

Lyn A. Sedwick, M.D.

Cat Scratch Disease Associated with Neuroretinitis in a 6-Year-Old Girl. Ulrich GG, Waeker NJ Jr., Meister SJ, Peterson TJ, Hooper DG. Ophthalmology 1992;99:246-9 (Feb). [Reprint requests to Dr. G. G. Ulrich, c/o Clinical Investigation Department, Naval Hospital, San Diego, CA 92134-5000.]

A 6-year-old girl with probable cat scratch disease developed a unilateral neuroretinitis which resolved to 20/25 acuity by 7 months later.

Lyn A. Sedwick, M.D.

Pupillary Constriction During Forceful Eyelid Closure. Cox TA, Digre KB. Am J Ophthalmol 1992;113:190-2 (Feb). [Reprint requests to Dr. T. A. Cox, Department of Ophthalmology, University of Utah Health Sciences Center, 50 N. Medical Dr., Salt Lake City, UT 84132.]

Thirty normal subjects were studied for pupillary response to eyelid closure. Nine had clinically detectable constriction with this maneuver. The authors recommend trying this technique to elicit pupil constriction in patients with "poor near response."

Lyn A. Sedwick, M.D.


A 21-year-old woman with several years history of visual loss left eye was found to have optic nerve enlargement on computerized tomographic scanning thought to represent glioma or meningioma. Progressive visual loss ensued to near blindness. Magnetic resonance imaging then showed an annular enhancing lesion, which extended into the chiasm. Surgical biopsy showed choristoma, that is, normal tissue in an abnormal location.

Lyn A. Sedwick, M.D.

Late Overcorrection of Hypotropia in Graves' Ophthalmopathy. Hudson HL, Feldon SE. Ophthalmology 1992;99:356-60 (Mar). [Reprint requests to Dr. S. E. Feldon, Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.]

The authors report on 5 patients from a group of 12 consecutive patients with hypotropia from thyroid eye disease who initially were well-corrected surgically but developed an overcorrection. They postulate that superior rectus contraction occurred because of tension postoperatively related to preoperative proptosis and superior rectus enlargement. The authors believe that their patients had stable measurements long enough preoperatively to obviate a contribution of active thyroid eye disease itself, but their preoperative stability was only, on average, 26 weeks.

Lyn A. Sedwick, M.D.

A 9-year-old boy fell on a toy spear tipped with a wooden golf tee. An intracranial wooden foreign body was not seen on an initial computerized tomographic study but was well-visualized on magnetic resonance imaging performed when his clinical status was deteriorating.

Lyn A. Sedwick, M.D.


A 58-year-old woman who had a nephrectomy for renal cell carcinoma and was on prednisone for autoimmune hemolytic anemia presented with a 3-week history of diplopia, left facial numbness, and left periocular and facial swelling. She had no light perception vision left eye with a pale disk and diffuse retinal edema consistent with arteriolar occlusion. In spite of aggressive diagnostic surgery and therapeutic maneuvers for mucor, the patient expired.

Lyn A. Sedwick, M.D.


A 16-year-old obese girl experienced abrupt visual loss right eye 2 weeks before examination, which disclosed bilateral decreased visual acuity, contracted visual fields, bilateral disk edema and a branch retinal arteriole occlusion right eye. Computed tomographic scanning was normal and lumbar puncture showed an opening pressure of 400 mmH₂O with normal fluid. She was aggressively treated with acetazolamide and methylprednisolone with good return of visual function. The authors believe her retinal arteriole occlusion was directly related to axonal swelling from papilledema.

Lyn A. Sedwick, M.D.


This editorial summarizes the results of the Optic Neuritis Treatment Trial which was fully reported in the New England Journal of Medicine February 27, 1992 (v. 326, pp. 581-8). Between 1988 and 1991, 457 patients were randomized to three groups: (1) placebo, (2) oral prednisone only, and (3) intravenous methylprednisolone for 3 days, followed by 11 days of oral prednisone. The group receiving oral prednisone had excess recurrent optic neuritis within the first 6 months of follow-up; only the group with intravenous steroid had a slightly better outcome in terms of visual function at the end of 6 months.

Lyn A. Sedwick, M.D.
Traumatic Intracanal Hematic Cyst of the Orbit.
Goldberg SH, Sassani JW, Parnes RE. Arch Ophthalmol 1992;110:378–80 (Mar). [Reprint requests to Dr. S. H. Goldberg, Department of Ophthalmology, Pennsylvania State University College of Medicine, PO Box 850, Hershey, PA 17033.]

A 35-year-old man presented with periocular pain 9 days after blunt orbital trauma. He had ptosis and computerized tomographic scanning demonstrated a posterior orbit cystic mass which at surgery proved to be a hematic cyst with some fresh blood. The authors believe theirs is the first reported case of an intracanal hematic cyst secondary to trauma.

Lyn A. Sedwick, M.D.