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Manuscripts should be submitted to J. Lawton Smith, M.D., Editor, 9820 S.W. 62nd Court, Miami, Florida 33156. Telephone: (305) 665-6827.

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Myasthenia Gravis and Charcot-Marie-Tooth Disease

In this issue of the Journal, Dr. J. R. Berger and associates report the case of a 68-year-old man with a typical history of Charcot-Marie-Tooth disease (peroneal muscular atrophy) that began with slowly progressive weakness in the legs at a youth, progressed to the degree that he was unable to work as a barber by age 36, and finally the diagnosis of Charcot-Marie-Tooth disease was made at age 42. In 1975, he developed impaired ocular gaze to the left, which responded to Tensilon, and a notable improvement in ocular motility was demonstrated on Mestinon therapy thereafter. Two years later, ptosis, hoarseness, dysphagia, and external ophthalmoplegia developed, and again there was a positive Tensilon test. Convincing clinical data confirmed the fact that this patient did indeed have both diseases, i.e., Charcot-Marie-Tooth disease and myasthenia gravis. The reason that this report is of particular interest is that reports of ocular findings mimicking myasthenia gravis have been made previously (Spector et al.1 and Brust et al.2) and Brust and associates3 also reported the case of a patient with Charcot-Marie-Tooth disease and ocular myasthenia gravis. What are these data saying? A fairly rare disease—Charcot-Marie-Tooth syndrome—has now been reported in three interesting relationships with myasthenia gravis. Peroneal muscular atrophy can at times look like myasthenia gravis, it can at times occur with ocular myasthenia gravis, and it can at times occur with generalized myasthenia gravis. Charcot-Marie-Tooth disease is of sufficient rarity, as is myasthenia gravis, that one begins to wonder if a possible relationship between these two disorders may not be worth investigating. At the least, this report should spur clinicians to make sure they do a particularly careful examination of the eyes of patients suspected of having Charcot-Marie-Tooth disease.

For the ophthalmologists reading this issue, a few words about Charcot-Marie-Tooth disease: Harrison's Principles of Internal Medicine (10th edition) lists eight genetically determined neuropathies, as follows.

I. Chronic familial polyneuropathies without a known associated metabolic disturbance
1. Peroneal muscular atrophy
2. Hereditary sensory neuropathy
3. Progressive hypertrophic polyneuropathy

II. Genetic polyneuropathies associated with a known metabolic disorder
1. Refsum's disease
2. Abetalipoproteinemia
3. Metachromatic leukodystrophy
4. Tangier disease
5. Familial amyloidosis with neuropathy

Principles of Internal Medicine describes Charcot-Marie-Tooth disease as a dominant hereditary disease with onset during adolescence or adulthood. Distal muscle atrophy, secondary to chronic degeneration of peripheral nerves and roots, begins in the feet and legs and later involves the hands. Early symptoms are muscular wasting and weakness, involving extensor and evertor muscles of the feet and producing an equinovarus deformity. Later, all muscles below the middle third of the thigh may atrophy, resulting in the classic "stork leg" or "champagne bottle" appearance. After a period of years, atrophy of hand and forearm muscles develops. Again, the wasting seldom extends above the elbows, just as it seldom goes above the middle third of the thighs. The feet are short and arched, sometimes with perforating ulcers. Pain, paresthesias, and cramps are common. The objective sensory disorder is usually rather slight, but is conspicuous enough to enable one to distinguish this syndrome from progressive muscular atrophy. Impaired position and vibratory sensation, and absent touch and pain sensation occur in the feet. Reflexes are absent in the involved limbs. The progression is very slow and it may be arrested at any stage. In families with onset during adolescence, nerve conduction velocities are very slow, and, pathologically, one sees hypertrophic neuropathy with "onion bulb" formation. In families with adult onset in the fourth or fifth decade, nerve conduction velocities are normal or minimally reduced and the pathology is that of axonal loss.
Eve signs are said to be infrequent with Charcot-Marie-Tooth disease, but a surprising number have been reported.\(^{1}\)

1. Retinitis pigmentosa
2. Papillary anomalies
3. External ophthalmoplegia
4. Nystagmus
5. Optic atrophy
6. Optic neuropathy
7. Leber’s optic neuropathy
8. Ptosis and ophthalmoplegia simulating myasthenia gravis
9. Associated ocular myasthenia gravis
10. Associated generalized myasthenia gravis

Walsh and Hoyt\(^{1}\) point out that onset occurs usually between ages 2 and 15, but may be deferred until the third decade. Wasting starts in the small muscles of the feet, then in peroneal muscles, then in the calf, forearm, and hand. The muscle atrophy progresses, foot drop develops, and, in rare instances, fibrillations are observed. The muscle atrophy tends to spare the thighs, hips, upper arms, and shoulders. The tendon reflexes are ultimately lost. Sensation often is not affected, ataxia is not observed, and the weakness and atrophy are usually symmetrical. However, Ford\(^{5}\) noted one leg and arm as being extensively involved several years before the opposite side was affected.

Mentality is normal, and sphincter control is preserved. Lemieux and Neeneh\(^{6}\) described an association between Charcot-Marie-Tooth disease and hereditary nephritis. A relationship between Charcot-Marie-Tooth disease and Friedrich’s ataxia has been noted repeatedly. Stephens\(^{7}\) reported a family of four generations with 63 members, and four in one generation had features of Friedrich’s ataxia, Charcot-Marie-Tooth disease, and external ophthalmoplegia.

Pleasure and Schotland\(^{8}\) in Merritt’s Textbook of Neurology (7th edition) describe peroneal muscular atrophy as including several genetic disorders of the peripheral nervous system that most severely involve the distal leg muscles. Inheritance is usually autosomal dominant but is less frequently autosomal recessive. Foot deformities are frequent and may be the only apparent feature of the disease in mildly affected family members. One may need to look at the feet of family members even if they are asymptomatic. Stacking-glove sensation impairment is usually present, but sensation is preserved in some families. Achilles reflexes are absent and other tendon reflexes may be diminished. Pleasure and Schotland differentiate two types of Charcot-Marie-Tooth disease on the basis of nerve conduction velocities and sural nerve biopsy. The axonal form (type I) shows motor and sensory nerve conduction velocities of less than 65% of normal and prolonged distal latencies; nerve biopsy shows segmental demyelination. The axonal form (type II) shows motor and sensory nerve conduction velocities of greater than 65% of normal; biopsy shows Wallerian degeneration to be most severe in distal nerve segments.

In type I Charcot-Marie-Tooth disease, symptoms begin in the first or second decade of life with foot drop and steppage gait. Distal atrophy produces the stork leg deformity and intrinsic hand muscle atrophy develops later. Distal reflexes are decreased or absent and stocking-glove sensory deficit is found. Scoliosis and high arches or clubbed feet are common. Peripheral nerves are often palpably enlarged. If an associated tremor is present, the constellation of Charcot-Marie-Tooth syndrome with tremor is called the Roussy-Levy syndrome.

In type II Charcot-Marie-Tooth disease, the first symptoms often appear in adulthood, although foot deformities may be evident much earlier. Atrophy, sensory changes, and depressed reflexes usually show less severe deficits than in type I, and nerves are not palpably enlarged. The spinal fluid protein level is frequently elevated in type I but is normal in type II Charcot-Marie-Tooth disease. The spinal fluid is otherwise normal. The differential diagnosis of peroneal muscular atrophy includes Friedreich’s ataxia, familial amyloidosis, Dejerine-Sottas disease, Refsum’s disease, lipomas and other masses in the lumbosacral canal, and myotonic muscular dystrophy. I have seen two brothers with Charcot-Marie-Tooth disease in whom there was an interesting association with Duane’s retraction syndrome. The Duane’s syndrome was unilateral in one brother and bilateral in the other. The point to be emphasized here is that every patient with suspected Charcot-Marie-Tooth syndrome merits a careful neuro-ophthalmologic examination. The ductions should be quantitated. Photographs of the lids and ocular rotations are helpful in the record.

Finally, every patient with ptosis and diplopia should have a Tensilon test. This continues to be an excellent clinical dictum. I believe I have seen a family with chronic progressive external ophthalmoplegia and ocular myasthenia gravis together. Dr. S. W. Clark of Waycross, Georgia, saw three brothers with a classic slow progression of ptosis and external ophthalmoplegia. A family photograph album documented the presence of the syndrome in several family members. When I saw one of them in consultation, the findings of chronic progressive external ophthalmoplegia or Kiloh-Nevin ocular muscle
dystrophy were so impressive that it was thought unnecessary even to do a Tensilon test. Dr. P. S. O'Connor reminded me of the dictum, however, and a Tensilon test was performed. To my amazement, there was an unequivocal improvement in ptosis and ocular motility in the patient after a dose of Tensilon. Careful clinical observations need to be continually made in neurologic diseases. We are grateful to Dr. Berger and associates for adding this additional interesting case to the literature.

J. L. Smith, M.D.
Myasthenia Gravis Complicating Charcot-Marie-Tooth Disease: Report of a Case

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Abstract
Generalized myasthenia gravis developed in a 61 year old man with the hypertrophic form of Charcot-Marie-Tooth disease (CMT). While ocular abnormalities mimicking myasthenia gravis have been reported in CMT, and two patients with atypical CMT have had features consistent with oculor myasthenia, this is the first report of generalized myasthenia gravis complicating CMT. The estimated prevalence for the concurrence of these two disorders suggests that it is an extremely rare event.

Eyelid ptosis1-4 and motility disorders1,2,4 consistent with ocular myasthenia have been observed in patients with Charcot-Marie-Tooth disease (CMT). In 1974, Brust and associates5 described a patient with ocular myasthenia and "complicated" CMT that was associated with spasticity of the lower extremities. A dramatic improvement in ptosis and extraocular motility was noted following prostigmine and edrophonium administration, but there was no response in limb weakness. We describe a patient in whom generalized myasthenia gravis was superimposed on classic CMT. The coexistence of these two relatively rare disorders in the same individual has not been previously reported.

Case Report
A 68-year-old, right-handed man recalled weakness dating to childhood. He commented on difficulty roller-skating, an inability to ice-skate because of ankle weakness, and frequent falling while playing soccer. As a young man he pursued a short professional boxing career. In the army, he was unable to march as well as the other troops and dropped out of line frequently due to leg weakness. Over the course of the next 15 years, he experienced a heavy sensation in the lower extremities associated with progressive weakness in the hands and legs. Within ten years, he was unable to walk without assistance. At age 36, he was forced to cease working as a barber and was subsequently confined to a wheelchair. At age 42, he was diagnosed as having Charcot-Marie-Tooth disease. Examination at that time revealed marked distal extremity wasting and weakness, areflexia, impaired distal extremity vibratory sensation, and palpably enlarged peripheral nerves. Cerebrospinal fluid was normal. His family history was negative for any neurological disorders.

In 1975, he developed progressive left-gaze palsy that typically worsened late in the day. Examination revealed weakness of the left lateral rectus and right medial rectus muscles. No other cranial nerve abnormalities were detected. The distal extremities were weak and atrophic. Loss of distal vibratory sensation and hypertrophic peripheral nerves were also noted. A diagnosis of ocular myasthenia was entertained, and after the administration of 10 mg intravenous edrophonium hydrochloride (Tensilon) he regained full extraocular motility. Nerve conduction studies revealed no detectable motor and/or sensory response on stimulation of the median, ulnar, peroneal, tibial, or sural nerves. On electromyography, positive waves and fibrillations were seen in the distal muscles of all extremities in the absence of motor unit potentials. The number of motor units was decreased in the proximal muscles. On routine study there

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was no evidence of a superior mediastinal mass and thyroid function was normal. Subsequently, the patient was placed on daily pyridostigmine (Mestinon), with a persistent and profound improvement in extraocular motility until 1977.

In 1977, bilateral ptosis, hoarseness, dysphagia and progressive dyspnea developed. Physical examination revealed a thin, debilitated man in mild respiratory distress. Bilateral ptosis was greater on the right than on the left, and there was paralysis of gaze in all directions. Facial diplegia was apparent and dysphonia and dysphagia were accompanied by an absent gag reflex. Motor examination revealed bilateral wrist and foot drop. He had a moderately severe distal and moderate proximal weakness involving the upper and lower extremities bilaterally. Bilateral rocker foot and "garter" type atrophy of the lower extremities were seen (Fig. 1). There was also diffuse atrophy of the distal musculature of the upper extremities. The disappearance of the thenar and the hypothenar eminences was noted, exposing the interosseous spaces in a "main de singe" fashion. The muscle tone appeared to be diffusely decreased and no muscle stretch reflexes were elicited. The vibratory sense was decreased symmetrically in the distal lower extremities. Hypertrophy of the greater auricular (Fig. 2), ulnar, superficial radial, saphenous, infrapatellar, and superficial peroneal nerves was noted bilaterally.

The Tensilon test was, again, dramatically positive, with marked improvement in the strength of the facial, extraocular (Fig. 3), and proximal limb muscles. Repetitive supramaximal stimulation of the accessory nerve at the rate of two per second resulted in a decremental response of 15% in the trapezius muscle. The test was partially corrected by Tensilon and after maximal voluntary contractions (MVC) for 30 s. Four minutes after MVC, a decrement of 30% was noted.

No sensory nerve action potentials could be elicited from the median, ulnar, radial, sural, or saphenous nerves. No motor response was obtained on stimulating the median, ulnar, peroneal, or tibial nerves. Stimulation of the accessory nerve produced a normal compound muscle action potential from the trapezius muscle. However, the latency was twice the normal value at 10.0 ms.

The diagnosis of myasthenia was reconfirmed by repeat Tensilon test. Anticholinesterase antibodies were present in high titer, although no thymoma was detected by radiographic means or by gallium scan. HLA typing revealed the following phenotype: A1, Aw24, Bw35, Bw40, Cw3, Cw4, DR2, and DR4.

Discussion

Ocular findings such as ptosis and abnormal extraocular motility, as well as facial di-
Myasthenia Gravis in Charcot-Marie-Tooth Disease

Figure 3. Bilateral ptosis (left) is dramatically improved immediately following the administration of Tensilon (right).

plegia, dysarthria, and bulbar weakness with dysphagia, have been reported to occur in CMT. The nature of these findings may suggest myasthenia gravis, but no response to anticholinergic medication is expected and repetitive nerve stimulation will not reveal a decremental response. Our patient had typical CMT with progressive lower extremity weakness dating back to age 19. Ocular myasthenia supervened at age 60 with the initial disturbance of a left-gaze palsy. Subsequently, the patient developed myasthenic weakness of the bulbar and extremity muscles, superimposed on the weakness attributable to the CMT. A marked improvement in ocular motility and proximal limb weakness following Tensilon administration, a decremental response to repetitive nerve stimulation, and a positive test result for anticholinergic receptor antibodies established the diagnosis of myasthenia gravis.

Although neurogenic muscle atrophy has been reported in myasthenia gravis, it is generally mild in degree. Consistent with these observations, evidence of a neuropathic process would not be anticipated prior to the clear-cut development of the myasthenia, as occurred in our patient. Garcin and colleagues described a man in whom progressive amytrophic weakness of the extremities followed by 20 years the onset of ptosis and extraocular motility disturbance. A positive response to neostigmine was noted in the eyes and limbs, and electrophysiological studies revealed a decremental response to repetitive stimulation. Despite their case report, clinically significant neurogenic muscular atrophy in myasthenia gravis is decidedly rare.

The prevalence of CMT varies with the population studied. Estimates of between 1.6 and 24 per 100,000 population have been reported, and a population study in North Carolina concluded that the prevalence was at least 5.4 per 100,000. The prevalence of myasthenia gravis ranges from 5 to 64 per million, with 40 per million being a conservative estimate. Assuming that the association of CMT and myasthenia gravis occurs randomly, their concurrence in the same individual would be seen with an approximate incidence of one in every 2 billion people.

Two individuals with hereditary neuropathies categorized as CMT have had ocular weakness responsive to cholinergic medication (Table). In both individuals, previously described, the CMT was atypical in nature. Although the patient described by Brust and colleagues displayed characteristics of ocular myasthenia, his CMT was unusual in that it was associated with a spastic paraparesis. Stevens described a patient with neostigmine-responsive ptosis. In addition to neuropathy with pes cavus, that patient exhibited periodic paralysis and myotonia. There was no comment mentioned of tests performed to confirm the existence of a neuromuscular transmission defect, and caution must be exercised in the presumption that neostigmine-responsive ptosis is sufficient for the diagnosis of ocular myasthenia.
in as much as positive responses to cholinergic drug administration have been recorded in other disorders\textsuperscript{14} such as amyotrophic lateral sclerosis,\textsuperscript{15} polymyositis,\textsuperscript{16} and botulism.\textsuperscript{17}

The syndrome of peroneal muscular atrophy associated with involvement of primary sensory neurons has been designated hereditary motor and sensory neuropathy (HMSN).\textsuperscript{18,14} In patients with severely decreased nerve conduction velocity, nerve biopsy shows extensive segmental demyelination and axonal loss. Hypertrophic changes may also be present. This type of peroneal muscular atrophy is referred to as the hypertrophic form of Charcot-Marie-Tooth disease\textsuperscript{20} or HMSN type I (HMSN I).\textsuperscript{19} Our patient's symptoms satisfied the criteria for the diagnosis of HMSN I. It is usually dominantly inherited, but autosomal recessive inheritance and a sporadic variety have been described.

To the best of our knowledge, there has been no previous description of a patient with classical CMT and well-documented generalized myasthenia gravis. Cholinergic drug administration and electrophysiological studies to look for evidence of a neuromuscular transmission defect characteristic of myasthenia gravis and assays of cholinergic receptor antibody would certainly be warranted in any patient with CMT presenting with ptosis, oculor palsies, facial diplegia, bulbar weakness, or fluctuating levels of extremity strength. The coexistence of myasthenia gravis and CMT in other individuals would suggest a more than chance association. HLA phenotyping in individuals with CMT may reveal an overlap with the phenotypes commonly observed in myasthenia gravis, namely, A1, B8, and Dw2.\textsuperscript{21}

References

June 1985

Berger et al.
Myasthenia Gravis in Charcot-Marie-Tooth Disease


Pseudohemangioma of the Optic Disc Following Ischemic Optic Neuropathy

J. LAWTON SMITH, M.D.

A 63-year-old woman with an elevated mass occupying the entire upper temporal quadrant of the left optic disc was examined in December 1974. The lesion resembled an angioma of the optic nerve by both ophthalmoscopic and fluorescein-angiographic criteria. Three months later, the lesion showed no change. However, at a routine follow-up in January 1976 the mass had disappeared. This occurred with no change in symptoms or visual function at all. The patient had previously suffered classic bouts of nonarteritic ischemic optic neuropathy in both eyes. She remained clinically stable thereafter on serial examinations for the next 5 years. This lesion may be called a "pseudohemangioma" of the optic disc. It has since been observed in other patients with previous bouts of optic nerve ischemia. The process may also be called "pseudoangiomatous hyperplasia" of the optic disc, or the "proud flesh syndrome." This report documents this interesting ophthalmoscopic observation to point out the importance of differentiating it from a true hemangioma of the optic disc, to comment on the pathogenesis of its development, and to consider the timing of its appearance and subsequent resolution in a few other cases.

Case 1

A 63-year-old right-handed white woman was first seen December 13, 1974, through the courtesy of Dr. Valberg of Ottawa, Canada. Her chief complaint was difficulty with vision in the right eye since 1968 and with vision in the left eye since July 1974. Present illness revealed that she had had no visual problems until June 1968, when she noted the onset of blurred vision in the right eye and was found to have a swollen optic disc and a lower altitudinal optic nerve fiber bundle visual field defect in that eye. The arterioles were narrowed on the disc, the disc rapidly became pale, and, although the field defect persisted, she was had 20/20 acuity in the eye and no subsequent change thereafter. She did well for the next 5 years until July 1974 (6 months before presentation), when she suddenly developed a superior altitudinal field defect in the left eye. She was hospitalized in Canada and was examined thoroughly, including roentgenography of the skull, chest, and optic foramina, a brain scan, and a lumbar puncture. The impression was of ischemic optic neuropathy. A short course of oral steroids at a modest dosage produced questionable improvement in the left eye. She had no other neurologic complaints. Her past history was otherwise unremarkable, while her family history was positive for diabetes mellitus in her mother.

An examination in December 1974 revealed a corrected acuity of 20/15 - 1 in the right eye and 20/25 + 1 in the left eye. Blood pressure was 170/100 in both arms. The visual fields revealed a dense, upper altitudinal defect in the left eye and a dense, lower nasal field defect in the right eye. Applanation tension was 12 in both eyes. Ophthalmoscopy revealed diffuse pallor of the right disc, without any particular atrophic cupping, and the arterioles were very narrow (Fig. 1). The left disc was pale, and there was an elevated mass on the upper temporal aspect between 12 and 3 o'clock (Fig. 2). On fluorescein angiography of the left disc, the mass resembled an angioma of the disc, filling in the arterial phase (Fig. 3) and staining in later phases (Fig. 4). The impression was of nonarteritic ischemic optic neuropathy with a pseudo-angiomia of the left optic disc.

At a follow-up examination 3 months later, the left disc appeared unchanged. However, at a follow-up examination on January 20, 1976, although no interval symptoms had occurred and acuity and fields were unchanged, the mass on the left disc had disappeared (Figs. 5-7). The patient was seen again in January 1977 and January 1978, with no further changes noted. Dr. Weiner saw her in January 1979 and found visual acuities of 20/20 in the right eye and
Pseudo-hemangioma of Optic Disc

Figure 1. Case 1. Right eye on December 13, 1974, showing changes of nonarteritic ischemic optic neuropathy that had occurred 6 years earlier.

20/25 in the left eye and noted that the fields and discs were unchanged.

Comment

A 63-year-old woman was seen in 1974. She had developed typical ischemic optic neuropathy in the right eye 6 years earlier and in the left eye 6 months prior to examination. She had excellent acuity but a lower-field defect in the right eye and an upper-field defect in the left eye. Routine examination 6 months after the episode in the left eye revealed an elevated mass lesion on the left disc that closely resembled a hemangioma of the optic disc by both ophthalmoscopy and fluorescein angiography. The lesion was unchanged 3 months later, but 13 months after the first examination the lesion was found to have spontaneously regressed to such a point that it had effectively disappeared. No subsequent change occurred in acuity, fields, or discs over the next 5 years. This was the author's first and most dramatic

Figure 2. Case 1. Left eye on December 13, 1974, showing changes of nonarteritic ischemic optic neuropathy that had occurred 6 months earlier. Note the elevated reddish mass on upper temporal margin of this disc (arrowheads).

Figure 3. Case 1. Fluorescein angiogram of left eye on December 13, 1974. Note that the mass on upper temporal disc fills in the arterial phase (arrowheads).

Figure 4. Case 1. Venous-phase fluorescein angiogram shows late staining of this vascular mass (arrowheads).

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Figure 5. Case 1. Left eye on January 20, 1976. Note that the mass on upper temporal aspect of this disc has essentially disappeared.

Figure 6. Case 1. $2 \times$ fundus photograph of left eye on December 13, 1974, showing large, elevated pseudohemangioma of the disc (arrowheads).

Figure 7. Case 1. $2 \times$ fundus photograph of left eye on January 20, 1976, showing that the mass has effectively disappeared. Only a few "ghost vessels" remain (arrowheads).

Figure 8. Case 2. Right eye in September 1984, showing a normal disc.

observation of pseudoangiomatous hyperplasia of the optic disc following ischemic optic neuropathy. A few milder cases are documented below to illustrate other points about this finding.

Case 2

A 62-year-old black man had been taking oral hypoglycemic drugs for diabetes mellitus for 5 years. On September 8, 1984, he noted the onset of a painless "shadow" before the left eye. Examination at the Bascom Palmer Eye Institute that day revealed a corrected vision of 20/25+ in the right eye and 20/60+ in the left eye. A lower altitudinal visual field defect was noted in the left eye. A 3+ Marcus Gunn pupil was present on the left. The right disc was within normal limits (Fig. 8). The left disc showed diffuse swelling of the entire upper temporal margin, with abnormal small vessels in that distribution and two small linear hemorrhages on the disc margin (Fig. 9). Exudative and lipid deposits were seen in the adjacent retina. On September 13, 1984, the corrected vision was 20/30 in the right eye and 20/100 in the left eye. Blood pressure was 164/90, sedimentation rate was 58, serum fluorescent treponemal antibody absorp-
Figure 9. Case 2. Left eye in September 1984, showing pseudoadangiomatous hyperplasia of upper temporal quadrant of the disc.

Pseudoadangiomatous hyperplasia of Optic Disc

Fluorescein angiography confirmed the presence of the pseudoadangiomatous hyperplasia of the entire upper temporal quadrant of the left disc (Figs. 10 and 11). On September 21, 1984, Dr. Darnley noted that the tuft of new vessels on the left disc above was still present but was starting to resolve.

Figure 10. Case 2. Left eye in September 1984, showing pseudoadangiomatous hyperplasia of upper temporal quadrant of disc and partial macular star figure. Two small hemorrhages are seen at 12:45 and 2 o'clock on the disc. Note abnormal vessels in this area (arrow).

It should be noted that the patient had had a routine eye examination at the Bascom Palmer Eye Institute on June 21, 1983, when he had lost his glasses. Corrected acuity was 20/25 in the right eye and 20/20 in the left eye, a dilated fundus examination at that time revealed healthy discs and no background retinopathy in either eye.

Comment

A 62-year-old diabetic man had normal optic discs in 1983. In September 1984, he developed acute ischemic optic neuropathy in the left eye, and the disc acutely showed pseudoadangiomatous hyperplasia of the upper temporal quadrant that was confirmed on fluorescein angiography. This case illustrates that the process under consideration can develop very rapidly in an ischemic disc.

Case 3

A 46-year-old right-handed white man had 20/20 vision in both eyes until November 23, 1975, when he awoke with blurred vision in the lower field of the left eye. This was painless, and it progressed over the next few days. He had no other complaints. He was examined at the Bascom Palmer Eye Institute on December 17, 1975, by Dr. J. W. Klein. Visual acuity was 20/15 in the right eye and 20/60 in the left eye. A 2+ Marcus Gunn pupil was present on the left. The visual field was normal in the right eye, but there was a lower altitudinal defect in the left eye. The right disc was normal (Fig. 12), but the left disc showed classic changes of acute nonarteritic ischemic optic neuropathy (Fig. 13). Fluorescein angiography showed some focal pseudoadangiomatous hyperplasia of left disc (Figs. 14 and 15) but was within normal limits of the right disc (Fig. 16). He was treated with a subtenon’s Kenalog injection, placed on Coumadin for 6 weeks, and he then took aspirin,
two per day, for the following year. Visual function remained stable for the next 7–8 years.

On February 24, 1984, when he was 55 years old, he noted an abrupt painless blurring of vision in his right eye while driving. Within a few days this became stable. An examination on September 17, 1984, revealed a corrected acuity of 10/200 in the right eye and 20/40 in the left eye. Altitudinal field defects were now present in both eyes. The optic discs in both eyes showed the late changes of ischemic optic neuropathy (Figs. 17 and 18).

**Comment**

The patient showed only mild pseudoangiomatous hyperplasia of the left disc at onset, confirmed by fluorescein angiography, but his case is described here because it documents the presence of a normal disc 8 years before onset of ischemic optic neuropathy in the right eye. It demonstrates the observation reported by Feit et al.¹ and Beck et al.² of a small, or absent, physiologic cup in an eye prior to a documented occurrence of nonarteritic ischemic optic neuropathy.

**Figure 12.** Case 3. Normal right optic disc on December 17, 1975.

**Figure 13.** Case 3. Left eye on December 17, 1975, showing changes of acute ischemic optic neuropathy.

**Figure 14.** Case 3. Arterial-phase fluorescein angiogram of left optic disc on December 17, 1975. Note poor filling of nasal vessels on disc surface.

**Figure 15.** Case 3. Late-phase fluorescein angiogram of left optic disc on December 17, 1975. Note late staining and some elevation of lower temporal aspect of the disc.
Case 4

A 56-year-old white man was examined on July 13, 1982, by the author along with Dr. E. W. D. Norton. The patient’s chief complaint was photophobia for 2 months and decreasing near vision for 2 weeks. The best corrected vision was 20/20 (–1) in both eyes. However, lower nasal arcuate scotomas were noted in both eyes. His blood pressure was 125/75 and the applanation tension was 13 in the right eye and 12 in the left eye. The optic discs in both eyes showed changes consistent with ischemic optic neuropathy. The right eye is shown in Figs. 19–21 and the left eye in Figs. 22–24.

Comment

A 56-year-old man presented with bilateral nonarteritic ischemic optic neuropathy of recent onset in both eyes. The focal disc changes under consideration were present in mild degree in both eyes. This case is described to show that the process can be simultaneous in both eyes.
Case 5

A 73-year-old white man was examined on April 23, 1984, by the author for Dr. Klingele. In September 1983, the patient awoke with painless blurring of vision in the left eye. Corrected acuity was 20/30 in the right eye and 20/50 in the left eye. An afferent pupil was noted on the left, altitudinal field defects were noted in both eyes, and both discs were swollen. He was admitted to Barnes Hospital on November 30, 1983, and treated with intravenous bolus steroids in high doses. He also had very narrow angles, for which a laser iridotomy was performed in the left eye. On the next day, the tension increased to 45 in the left eye and was controlled medically.

An examination in April 1984 revealed a corrected acuity of 20/30 in the right eye and 20/40 in the left eye. The blood pressure was 120/78. The tension was 19 in both eyes by applanation, and was 24 in both eyes after dilatation. The fundi revealed interesting changes thought to be consistent with pigmented paravenous choriotinal atrophy in both eyes. There were also changes on the lower temporal margin of the right disc thought to be consistent with the proud flesh syndrome; this was interpreted as having followed recent ischemic optic neuropathy in the right eye. The patient also had shallow anterior chambers and was status post-laser iridotomy in the left eye, which was considered probably not patent. Photographs of the
Pseudohemangioma of Optic Disc

Figure 24. Case 4. Later-phase fluorescein angiogram of left eye on July 13, 1982. Note that the two areas of disc staining are easier to see than in earlier views (arrowheads).

right disc and its fluorescein-angiographic appearance are seen in Fig. 23; the left eye is shown in Fig. 24.

Comment

A 73-year-old man presented with a complicated eye problem, having pigmented parafoveal chorioretinal atrophy in both eyes and then experiencing an attack of ischemic optic neuropathy in the right eye, with a tendency to angle closure glaucoma as well. The author has seen a patient who suffered a classic bout of nonarteritic ischemic optic neuropathy during an acute attack of angle closure glaucoma, who was later treated by bilateral peripheral iridectomies. It is important to recognize that ischemic optic neuropathy can rarely be caused by angle closure glaucoma, as iridectomy may prevent the occurrence of the problem in such cases. This case illustrates the fact that pseudoangiomatous hyperplasia can occur in patients who have other types of concomitant eye disease; its description can be helpful in establishing the diagnosis of ischemic optic neuropathy in similar clinical settings.

Discussion

Ischemic optic neuropathy is a very common entity in neuro-ophthalmological practice and has become well recognized since it was first reported in 1966. The form not associated with temporal arteritis is the most common. It is marked by the abrupt onset of painless blurring of vision in one eye in a middle-aged, healthy adult. Central vision is often spared initially, but there typically is a rather profound altitudinal visual field defect, which usually is permanent. After a delay of as much as several years, the second eye often becomes symmetrically involved in as many as perhaps half of cases. Although the patients are usually in excellent general health, about one-half will have mild hypertension and/or a family history of diabetes. It is important to reassure the patients that a second attack virtually never occurs in the same eye once the disease has stabilized (usually within 3 months of onset). The author may have seen the extremely rare exception to this rule in a recent patient of Dr. James Mitchell, but it remains a helpful clinical point. Hypertensive optic neuropathy may recur in the same eye and has some clinical similarities.

The ophthalmoscopic criteria of ischemic optic neuropathy are of interest. Initially, a typical pallid swelling, originally termed "pseudo-papillitis vasculaires" by Francois et al., is seen, but this rapidly progresses into an atrophic disc, often showing narrow arterioles and segmental or altitudinal pallor. The sharply altitudinal atrophy and its related field defect have not, to my mind, been adequately explained, despite numerous investigations of blood supply of the optic nerve head. However, the point under discussion here relates to focal changes in the disc both early and late in the evolution of the acute disc swelling in these patients.

One might consider the process simply as "luxury perfusion" of the disc. However, with careful Hruby lens study there are other aspects that need to be considered. What is being luxuriously perfused? One can see optic nerve disease presenting with simple hyperemia (i.e., vasodilation and prominence of normally preexisting small vessels on the disc margin). One can also see neovascularization on the disc margin or surface, which can be a proliferation of rather normal-appearing small vessels or obviously abnormal-appearing microtelangiectatic or aneurysmal small vessels. One can also see combined proliferation of capillaries and glial tissue, causing a focal swelling of the disc margin, as seen in some of the cases described here, and, uncommonly, the process can produce a notably elevated mass on the disc that can closely mimic a true hemangioma of the optic disc.

There are interesting questions that can be asked about the pseudohemangioma of the optic disc following ischemic optic neuropathy. Was the lesion in case 1, seen 6 months after the disc ischemia, a residual area of swelling from the original event, or had the swelling resolved and this tumefaction subsequently appeared? Interval observations were not available in case 1 to answer this question. The presump-
tion would be that this was truly a residual swelling from the original ischemic event, but why did the rest of the disc margin clear so rapidly and yet leave this impressive mass 6 months later? What is the mechanism of production of this degree of proliferation of capillaries and glial tissue? Is it due to axoplasmic flow stagnation? Is there a local action of angiogenesis induction factor operating on the optic nerve in such cases?

The cause of pseudohemangioma of the optic disc is unknown at this time, at least to the author. It is important to examine these discs with the Hruby lens to see the changes discussed, for they usually are totally missed by indirect ophthalmoscopy and can be overlooked on routine fundus photographs unless $2 \times$ magnification views of the discs are ordered. It is evident that one can differentiate the pseudohemangiomas of the optic disc from true capillary hemangiomas of the disc not only by a history of previous ischemia but also by the spontaneous disappearance of the pseudohemangioma over time. It is hoped that further study of the nature of these focal disc changes will help elucidate the pathogenesis of the rare instances in which the process can mimic a hemangioma.

References

Atypical Visual Prognosis with an Optic Nerve Glioma

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Abstract
A 13-year-old girl presented with a 1-year history of gradual decline of vision in her right eye. She was diagnosed by clinical examination and computed tomographic scan as having a right optic nerve glioma. While awaiting surgery, she experienced spontaneous improvement of her symptoms. Four years after the onset of symptoms, the Snellen acuity, color testing, and visual fields have returned to normal, while the computed tomographic appearance of the tumor is essentially unchanged. Possible mechanisms for such a fortuitous outcome are discussed.

In the last few decades, as our understanding of the biology of gliomas of the anterior visual pathway has grown, so has controversy regarding the appropriate therapy for these tumors. While most accept these lesions as benign hamartomas, there are occasional lesions that behave more aggressively. Nonetheless, in the era of computed tomography (CT), most physicians would clinically and radiologically follow an optic nerve glioma if there were no sign of impending chiasmal involvement or unmanageable proptosis. A recent report has used third- and fourth-generation high-resolution CT scans to clarify the radiologic criteria for the diagnosis of optic nerve glioma. This may, in many cases, obviate the need for biopsy expressed in some of the earlier reviews. We report our experience in a patient in whom serial observation of the tumor had a fortuitous outcome.

Case Report
A 13-year-old girl was referred because of 1 year of intermittent blurring of vision in her right eye. Whereas she did not know whether it had progressed, serial vision screenings at school and by her ophthalmologist had revealed a gradual decline in Snellen acuity over 1 year. There were no other symptoms. General medical history and examination were unremarkable. She began menstruating at age 10 and continued to have normal menses. A CT scan had been done (Figs. 1a and 1b) and showed a diffusely enlarged right optic nerve from the orbital apex to the globe and through a widened optic canal.

Initial neuro-ophthalmic examination in March 1981 revealed best-corrected Snellen acuity of 20/200 OD and 20/20 OS. American Optical pseudoisochromatic color plates were 1/6 in the right eye and 6/6 in the left eye. Arden gratings were consistent with decreased contrast sensitivity in the right eye, with sparing of the lower spatial frequencies. The left eye was normal. The visual field was normal in the left eye, and there was a dense central scotoma and an enlarged blind spot in the right eye (Fig. 2, top). The pupils were 4 mm round and reactive to light in both eyes, with a right afferent pupillary defect. The extraocular versions, saccades, pursuit, and optokinetic nystagmus were intact. The anterior examination was normal, and exophthalmometry revealed no proptosis. The fundus examination of the right eye showed gray-white pallor of the inferotemporal disc, with ruts in the inferotemporal nerve fiber layer and edema of the superior and nasal portions of the disc and nerve fiber layer. There were no spontaneous venous pulsations, but the veins did collapse with gentle digital pressure. The left fundus was normal.

When admitted to the hospital for surgical excision of the optic nerve glioma a few weeks later, the patient's vision had improved to 20/80 OD. Because of this spontaneous improvement, a decision to discharge her and follow up with frequent examinations was made. One month later, her vision was 20/60 + 2 in the right eye. The color testing and pupillary responses were unchanged. The visual field in the left eye was
the same, but the right eye now showed a small paracentral arcuate scotoma (Fig. 2, middle). The fundus of the right eye showed white temporal pallor with a diffusely thinned and edematous nerve fiber layer. Four months later, the Snellen acuity was 20/50 OD. One year after her initial presentation, the Snellen acuity was 20/40 OD and 20/20 OS, with color testing improving to 4/6 corrected in the right eye. The visual field now showed a small paracentral scotoma to a 2-mm white test object (Fig. 2, bottom). The afferent pupillary defect was present but less obvious. The fundus revealed moderate temporal pallor with diffuse thinning of the nerve fiber layer, more noticeable temporally. Spontaneous venous pulsations were present and there was no nerve fiber layer or disc edema. A CT scan done in September 1982...
showed a fusiform lesion extending to the supraserellar cistern (Fig. 1c).

Examination in September 1983 revealed a Snellen acuity of 20/20 OU. The visual fields were full to a 2-mm white test object and the color plates were 6/6 OU. A + right afferent pupillary defect persisted. When she was last examined in September 1984, the patient's vision was 20/15 OU with full fields to a 1-mm white test object. A CT scan done at that time was unchanged from the prior study (Fig. 1d).

Discussion

Whereas there have been a few reports of stable vision or spontaneous improvement of vision in patients with chiasmal gliomas, we found in the literature only two cases of patients
Figure 2. Serial visual fields. Top: March 1981. Middle: May 1981. Bottom: April 1982. In all three fields, solid lines and solid shading represent testing with a 5-mm white test object, and dotted lines and cross-hatching represent testing with a 2-mm white test object. All fields done at a 1-m test distance.
with an optic nerve glioma who demonstrated visual improvement without surgery or radiation therapy. Wright et al. reported a case of a child with an optic nerve glioma whose vision responded to patching therapy alone. Anderson et al. reported the case of a child with an optic nerve glioma that was diagnosed 6 years after a 2-week episode of decreased vision of unknown etiology. There is also a case report of a child who presented with a 1-month history of headaches and who was found to have proptosis and papilledema of the right eye, with best-corrected Snellen acuity of 20/20-2 OD and 20/25 + 1 OS, and a histologically verified right optic nerve glioma. This child never had loss of vision.

We believe that this is the first documented case report of a tumor that meets the criteria for CT diagnosis of an optic nerve glioma as reported by Jakobiec et al., that has shown dramatic recovery of visual function without surgery or radiation therapy. As the lesion certainly did not regress on the CT scan, the mechanism by which the tumor's effect on the optic nerve fluctuates is not clear. Goodman et al. has shown in his case of a large optic nerve glioma with normal vision that, although there was demyelination present, the architecture of the nerve was preserved. Our case proves that the presence of an optic nerve glioma does not de facto rule out the return of visual function. A possible mechanism for fluctuation of vision is that as myxomatous changes are known to occur within optic nerve gliomas, and as the quantity of the hydrophilic extracellular mucus can vary relatively rapidly, perhaps the water content of these tumors varies and causes fluctuating compression and dysfunction of the remaining neural elements. Furthermore, in a child of this age, perhaps some endocrine function allows for variable vascular engorgement of the glioma. We feel that this case reaffirms the view that in a painless eye with a tumor that meets the CT criteria for the diagnosis of an optic nerve glioma, regardless of the visual acuity, repetitive neuro-ophthalmologic examination and periodic CT scanning is a viable alternative to surgery or radiation therapy.

References

Neovascular Glaucoma as a Complication of the Wyburn-Mason Syndrome

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Abstract
A child with the Wyburn-Mason syndrome developed neovascular glaucoma in association with changes in the retinal arteriovenous malformation and signs of retinal and choroidal ischemia.

The Wyburn-Mason syndrome is a rare congenital anomaly consisting of arteriovenous malformations involving the retina and central nervous system. The intracranial malformation may hemorrhage, but the retinal lesion is usually stable. Occasionally, retinal hemorrhage and exudation from the retinal arteriovenous communication occur. Although in some cases capillary nonperfusion has been documented by intravenous fluorescein angiography, to the best of our knowledge, iris neovascularization and glaucoma have not previously been reported. We describe what we believe to be the first case of rubeosis iridis and neovascular glaucoma in a patient with Wyburn-Mason syndrome who had severe ischemia of both the retinal and choroidal circulation.

Case Report
A 4-year-old white girl was referred to the Cleveland Clinic Foundation in March 1981. A diagnosis of amblyopia of the left eye had been made when the child was 3 years of age. Past medical and family histories were noncontributory.

Initial ocular examination at the Cleveland Clinic revealed right eye vision of 20/30 and left eye vision of 20/200. The complete examination was normal, except for a 3+ afferent pupillary defect on the left, 3.5 mm of proptosis of the left eye, and a vascular anomaly consisting of a large dilated vessel inferotemporally on the left disc (Fig. 1).

Neurologic examination was remarkable only for a bruit over the left mastoid and supraclavicular areas.

High resolution computed tomography (CT) scanning of the orbits and parasellar region with and without contrast enhancement demonstrated a dilated vascular mass in the posterior portion of the left orbit extending into the suprasellar cistern. Digital subtraction angiography showed a vascular mass in the left retro-orbital space. A conventional angiogram of the left internal carotid artery revealed an arteriovenous malformation in the posterior aspect of the left orbit, and suprasellar region supplied primarily by the ophthalmic artery (Fig. 2). Based on the clinical and angiographic findings, a diagnosis of Wyburn-Mason syndrome was made.

On a routine follow-up examination 15 months later, visual acuity of the left eye and exophthalmometry measurements were unchanged. Repeat fundus examination demonstrated a change in the appearance of the arteriovenous malformation, with further dilation of the arteriovenous loop inferiorly and newly dilated vessels on the superior portion of the optic disc (Fig. 3).

On November 15, 1982, the patient was seen for a red, painful left eye of 2 days’ duration. Visual acuities were 20/20 in the right eye and counting fingers at 1 ft in the left eye. Exophthalmometry measurements were unchanged. Slit lamp examination showed diffuse microcystic corneal edema and mild anterior chamber reaction consisting of a few cells and
trace flare, in addition to neovascularization of the iris. Applanation tension of the left eye was 52 mm Hg. Fundus examination of the left eye revealed disc edema, posterior pole retinal hemorrhages, beading and dilation of the retinal veins, extreme narrowing of the retinal arteries, and choroidal infarcts in the midperiphery (Fig. 4). The anomalous vessels on the optic disc were further dilated. Gonioscopy showed that the anterior chamber angle was closed almost 360° with neovascularization. The bruit over the left mastoid and supraclavicular areas could no longer be heard.

A diagnosis of neovascular glaucoma with both retinal and choroidal ischemia was made. The intraocular pressure was brought under control with intravenous Diamox, and topical Timoptic, epinephrine, and pilocarpine. Intravenous fluorescein angiography showed diffuse choroidal fluorescence in the posterior pole of the left eye, with complete filling of the anomalous vessels on the optic disc but no filling of the remaining retinal vessels 15 min after injection.

On November 18, 1982, panretinal xenon laser photocoagulation was performed under general anesthesia. A repeat left internal carotid angiogram demonstrated no significant change in the orbital and suprasellar vascular malformation.

On follow-up examination approximately 3 weeks later, the visual acuity was light perception. The iris rubeosis was markedly decreased and the applanation pressure was 10 mm Hg. A repeat fluorescein angiogram showed some decrease in size of the anomalous vessels on the optic disc and also diminished profusion of these (Fig. 5). On subsequent follow-up examinations, the eye has become prephthisical.

Discussion

In reviewing this case of Wyburn-Mason syndrome, we note two interesting features: the
change in the size and configuration of the retinal arteriovenous malformation and the development of rubeosis iridis and neovascular glaucoma.

The visual acuity in the Wyburn-Mason syndrome may range from normal\(^5\) to no light perception.\(^5\) A homonymous hemianopia may occur as a result of the intracranial portion of the arteriovenous malformation.\(^9\) The retinal portion may produce decreased vision either by cystic retinal degeneration\(^2\) or vascular decompensation.\(^5\)

The case we describe demonstrated spontaneous change in the size of the retinal arteriovenous malformation (Figs. 1, 3, and 4). Whether this change represented primary growth of the arteriovenous malformation or a disturbance in vascular hemodynamics with either increased or reduced flow is not known. Spontaneous regression and enlargement of these retinal arteriovenous malformations have been documented.\(^10\)-\(^13\) Augsburger and co-workers\(^12\) described the changing appearance of a complex retinal arteriovenous malformation over a 17-year period. While one portion of the malformation underwent spontaneous obstruction, another portion underwent marked elongation, tortuosity, and dilation.

Another unusual feature of this case was the development of rubeosis iridis and neovascular glaucoma, which to our knowledge has not been previously reported in the Wyburn-Mason syndrome. We suggest that ocular ischemia played an important role in the development of the iris neovascularization in this case, as is sometimes seen in central retinal vein occlusion and diabetic retinopathy.

Ashton\(^11\) proposed that the ischemic retina produces a vasculogenic factor that can diffuse anteriorly to produce iris neovascularization. The choroidal infarcts noted in our patient may also have contributed to the development of rubeosis iridis.\(^11\)

To explain the presence of ocular ischemia in our patient, two mechanisms may have been operative. If the arteriovenous malformation supplied part of the arterial circulation to the retina and choroid, then a partial thrombosis of the malformation could have produced ocular ischemia. Alternatively, increased flow and an
Neovascular Glaucoma in Wyburn-Mason Syndrome

enlarging arteriovenous malformation could have led to a change in hemodynamics, resulting in a "steal" phenomenon with decreased flow to the arteries supplying the retina and the choroid. This concept of steal with subsequent ocular ischemia and rubeosis iridis has previously been proposed by Huckman and Haas.¹⁵ They reported two cases of internal carotid artery occlusion complicated by neovascular glaucoma in which retrograde flow in the ophthalmic artery was documented by carotid arteriography.

We feel that it is important to note that the arteriovenous malformation of the Wyburn-Mason syndrome may change in size, probably because of altered hemodynamics. Therefore, intravenous fluorescein angiography with specific attention to intraretinal circulation and chorioidal flow patterns should be of help in detecting changes indicative of abnormal perfusion of the posterior pole and thus in managing and preventing rubeosis iridis and neovascular glaucoma. If the development of rubeosis iridis could be anticipated, it could be treated at an earlier stage.

In summary, this case demonstrates that rubeosis iridis and neovascular glaucoma may occur in association with changes in the ocular arteriovenous malformation of the Wyburn-Mason syndrome.

References

Paraneoplastic Tonic Pupils*

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Abstract
Tonic pupils developed in two patients with malignancies outside the nervous system. Symptoms and signs of more generalized somatic and autonomic nervous system involvement were also present. Although the exact morphologic basis for autonomic dysfunction in patients with paraneoplastic neurologic deterioration is uncertain, recent studies suggest that in some cases an autoimmune mechanism is responsible and may be directed against autonomic ganglia.

Autonomic neuropathy is an uncommon complication in patients with cancer and usually occurs as a so-called remote effect of the underlying neoplasm.1-4 Orthostatic hypotension is the most frequently reported sign of autonomic insufficiency.1-3,5,6 However, cancer patients may present a spectrum of dysautonomia, ranging from pandysautonomia7 to relatively selective involvement of bladder,8,9 gastrointestinal tract,10,11 or the sudomotor system.5,9,13 We report the cases of two patients with malignancies in whom tonic pupils developed as an early and prominent feature of presumed paraneoplastic neurological deterioration.

Case 1
A 32-year-old man complained of a distortion of smell and taste associated with anorexia, nausea, and vomiting after meals. A dysesthetic sensation was present over the left posterior scalp. One month later, vision in the left eye became blurred. An examination by an optometrist documented normal acuity but a "relative mydriasis with a poor reaction to light" in that eye. Over a 2-month period, reading became difficult. Feelings of stiffness and tingling appeared in the left arm and leg. Postprandial vomiting continued and a weight loss of 38 lb was documented. Medical evaluation showed routine blood cell counts, blood chemistries, electroencephalogram, and computed tomography (CT) head scans were normal. However, cerebrospinal fluid examination showed elevated protein level (242 mg%), with a normal glucose level and only two lymphocytes. The patient was transferred to our hospital for evaluation.

Examination showed a cachectic man who appeared depressed. He complained of visual blurring and acral paresthesias. The general examination was considered normal. Neuroophthalmologic examination showed that the right pupil was 4 mm and reactive to light. The left pupil was 5 mm and reacted poorly to both light and accommodation. Neither pupil constricted following instillation of dilute pilocarpine. Visual acuity, visual fields, and ocular mobility were normal. The left arm and left leg were weak, and position, vibration, and pain sense were diminished on that side. Dysmetria was also present on the left and seemed disproportionate to the degree of weakness. Deep tendon reflexes were exaggerated in the right arm and leg and absent at the left knee and ankle.

Routine blood cell counts, chemistries, and urinalysis were normal. A VDRL test was non-reactive. The erythrocyte sedimentation rate was 23 mm/h. Thyroid studies, antinuclear antibodies, heterophil titers, serum and urine immunoelectrophoresis, urine analysis for heavy metals and arylsulfatase, and Cortrosyn stimulation were normal or negative.

*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of Defense or the Uniformed Services University of the Health Sciences. Write for reprints to: C. G. Maitland, M.D., Tallahassee Neurological Clinic P.A., 1401 Centerville Road, Suite 300, Tallahassee, FL 32308, U.S.A.
Repeat lumbar puncture showed a protein level of 372 mg\(\text{dL}^{-1}\), with a normal glucose level. Two lymphocytes were present. Bacterial and fungal cultures showed no growth. Oligoclonal bands and myelin basic protein were absent. CT head scans were normal, as was a muscle biopsy. Sural nerve biopsy showed only mild, nonspecific myelin disruption and axonal loss. Electroneuromyography showed unobtainable sensory nerve action potentials. H reflexes, and blink reflexes in the extremities and face. In contrast, distal motor latencies, including facial nerve latencies, and conduction velocities were normal. These findings were felt to be consistent with prior reports of sensory neuropathy associated with a remote effect of carcinoma. However, cerebrospinal fluid cytology, chest roentgenograms, upper and lower gastrointestinal series, intravenous pyelography, gallium scans, and bone marrow biopsy were normal. 

Weight loss continued despite hyperalimentation and an empiric trial of steroids. Near vision became more blurred. Examination 5 months after symptoms began showed that the right pupil was dilated, irregular, and fixed to light and accommodation. The left pupil was 1 mm smaller and irregular. Light–near dissociation was present in the left pupil and slow tonic redilation followed strong accommodative effort. Slit lamp examination demonstrated segmental iris contraction. Instillation of dilute pilocarpine again produced no response. During the next 4 weeks, subtle light–near dissociation appeared in the right eye as well. Instillation of dilute (0.125%) pilocarpine now produced brisk pupillary responses in both eyes (Figs. 1 and 2). Further testing of autonomic function showed norothesstatic change in blood pressure and physiologic changes in pressure and heart rate with Valsalva’s maneuver. Urologic examination showed normal bladder function. Schirmer’s test was normal and fungiform papillae were present on the tongue. Sweating was intact over the face and body.

Eight months after symptoms first appeared, the patient complained of low midline abdominal pain. Proctoscopy with biopsy showed a 2-cm polyp with malignant change. Following pelvic irradiation, a colectomy was performed. Pathologic examination showed an adenocarcinoma, arising within a villous adenoma, with penetration into the lamina propria of the sigmoid colon (Fig. 3). Regional nodes were negative for tumor. However, after several months, abdominal CT scans demonstrated recurrent neoplasm encroaching on the retroperitoneal space and kidney.

**Case 2**

A 61-year-old woman complained of light-headedness upon standing and of dysesthesias in both thighs. Over a 3-month period, the lightheadedness became more severe and the patient occasionally fainted. Protracted nausea and vomiting developed and she lost 50 lb. Diagnostic tests reputedly showed only a hiatal hernia.

Two months later, the patient complained of blurred vision, and she could no longer read. Speech became slurred and swallowing difficult. Her face and tongue felt numb; shortly thereafter, ascending numbness of both lower extremities developed.

Examination showed a cachetic-appearing woman. Blood pressure was 140/100 supine, dropped to 80/70 immediately upon standing, and soon after became inaudible. The pulse rate remained fixed at 120 beats/min in all positions. No beat to beat variability appeared with Valsalva’s maneuver. The general examination was considered normal otherwise. Neuro-ophthalmologic examination showed that the right pupil was 6.5 mm and the left pupil was 5.5 mm. Neither pupil reacted to light. Convergence effort was poor and no near response could be seen. Instillation of dilute pilocarpine (0.125%) produced brisk constriction of both pupils. Visual acuity was 20/30 OU and ocular motility was normal. The corneal reflexes were absent and pain sensation depressed in the V2 and V3 distribution bilaterally. Both pterygoid and tongue muscles were weak, and speech was slurred. A dense sensorineural hearing loss was present in both ears. Generalized muscle wasting was evident. Deep tendon reflexes were absent. A patchy sensory loss was present in the upper extremities and pain sensation was reduced in a stocking-glove distribution in the lower extremities.

Diagnostic blood tests revealed anemia and thrombocytosis. Chest roentgenograms showed a subternal nodular density. Pathologic examination of a specimen of the lesion obtained by transmediastinal needle biopsy demonstrated oat cell carcinoma. Examination of cerebrospinal fluid was normal. No malignant cells were seen.

Two years later, examination showed the patient to be wheelchair-bound with severe orthostatic hypotension. Her right pupil was now 4.5 mm and her left pupil was 3.0 mm. Neither pupil reacted to light, but both displayed spontaneous variability in size (up to 1.5 mm) over a 1-h period.
Discussion

Parasympathetic pupillary dysfunction associated with malignancy outside of the orbit and nervous system occurs rarely. Baumann found, at autopsy, degeneration of dorsal root ganglion cells and posterior columns in a patient with lung cancer and a severe sensory neuropathy. The patient had had dilated, unreactive pupils. Schuffler et al. noted “Adie’s pupil reaction” in a patient with intestinal pseudo-obstruction and small cell carcinoma of the lung. No further mention of visual or ocular motor function was made. Beallo described bilateral tonic pupils in a patient with a myasthenic syndrome due to oat cell carcinoma of the lung. Our first patient developed light–near dissociation of first the left and then the right pupil, associated with symptoms of accommodative insufficiency, over a 6-month period. Slit lamp examination and pharmacologic testing demonstrated features typical for tonic pupils. Our second patient also had light-fixed pupils and reported symptoms consistent with accommodative insufficiency. Poor convergence effort precluded testing for tonic pupillary redilation. However, instillation of dilute pilocarpine produced brisk pupillary constriction, a finding ordinarily considered pathognomonic for denervation supersensitivity.

The term “tonic pupil” describes clinical findings associated with damage to the ciliary gan-
Paraneoplastic Tonic Pupils

Figure 2. Case 1. Right pupil at rest and following instillation of dilute pilocarpine. Note flattening of pupillary margin from 2 to 5 o'clock, indicating sector palsy of the sphincter (left). Brisk constriction follows drug administration (right).

glion and/or postganglionic parasympathetic innervation of the intraocular muscles. Tonic pupils may result from local ocular or paraoocular disease processes, as a component of a widespread peripheral neuropathy, or as a part of “Adie’s syndrome,” a combination of tonic pupils of obscure origin and impaired tendon reflexes of the limbs. Pupillary dysautonomia in our patients was accompanied by symptoms and signs of more generalized somatic and au-

Figure 3. Case 1. Pathological specimen taken from the sigmoid colon showing adenocarcinoma arising in a villous adenoma (lower right) with partial penetration of the lamina propria.
tonomic nervous system dysfunction related to an underlying neoplasm. Visual symptoms due to internal ophthalmoplegia preceded discovery of an occult malignancy in both cases. Neither patient exhibited signs of orbital disease or dysfunction of ocular muscles besides the pupils. In one case, tonic pupils evolved over a few months as part of a generalized neuropathic process, and at a rate significantly faster than is seen with Adie’s syndrome. In the second case, symptoms of accommodative insufficiency appeared at about the same time that orthostatic hypotension developed. Although patients with Adie’s syndrome occasionally exhibit other signs of autonomic insufficiency, orthostatic hypotension is rare.

In cases of paraneoplastic nervous system deterioration, there is neuronal and axonal degeneration in various parts of brain, long spinal tracts, and in ganglia. Infiltration of nervous tissue with lymphocytes, plasma cells, and histiocytes suggests either a response to direct viral invasion or an immunologic response, somehow initiated by tumor and directed against normal tissue.

In some cases with autonomic nervous system involvement, an autoimmune mechanism is possible and may be directed against autonomic ganglion cells. Bell and Seetharam demonstrated that small cell lung carcinomas regularly possess characteristic antigenic determinants that are also expressed in neurons of parasympathetic myenteric plexi. Infiltration of pseudo-obstruction, associated with pathologic findings of inflammatory infiltration and neuronal degeneration within myenteric plexi, occurs occasionally in patients with malignancies outside the gastrointestinal system. Somatic ganglia may also be involved. Graus et al. found an antibody specific to nuclei of neurons of the dorsal root ganglion in the serum of a patient with oat cell carcinoma and a subacute sensory neuropathy. Dowling and Cook also found dorsal root ganglia antibodies in 60% of a small series of patients with nonmetastatic neurologic syndromes associated with carcinoma. Electrodiagnostic studies in our first patient suggested that the likely site of involvement was at or near the level of the sensory ganglia. The patient's subacute sensory neuropathy with elevated cerebrospinal fluid protein level was similar to neuropathies reported in other patients with carcinoma. Baumann and Horwich et al. found inflammation and degeneration of dorsal root ganglia, posterior roots, and posterior columns in such cases.

An immune mechanism directed against ganglion cells is found in at least one other disease. Keane described tonic pupils in a patient with Guillain-Barré syndrome, a disorder felt to be autoimmune in nature. Dowling and Cook subsequently demonstrated antibodies to monkey dorsal root ganglia in sera from patients with inflammatory polyneuropathies. Hodson et al. found extensive neuronal destruction of dorsal root ganglia in a patient with Guillain-Barré syndrome, associated acute dysautonomia, and fatal myocarditis. Nevertheless, the exact morphologic basis for involvement of dorsal root and parasympathetic ganglia in paraneoplastic syndromes is unclear. Antigenic determinants common to ganglion cell body and tumor cell may play a role. Direct viral invasion of gangliionic tissue remains an unproved possibility. Regardless of the exact pathophysiology, tonic pupils may signal the presence of an underlying malignancy, particularly if pupillary abnormality develops rapidly or is associated with other signs of neurologic deterioration.

Acknowledgment

Appreciation is expressed to Dr. Mary Bibro of the Department of Laboratory Medicine, National Hospital, Bethesda, for her help with the pathology specimens. We also wish to thank Mrs. Ferne Robinson for assistance with manuscript preparation.

References

Paraneoplastic Tonic Pupils


Unilateral Pupillary Distortion:
A Case Report

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Abstract
A 29-year-old white man who complained of episodic pupillary distortion in his right eye brought on by strenuous exercise was found to have a segmental Horner's syndrome in association with a hypoplastic internal carotid artery.

There is a rare but interesting phenomenon that has been reported in which intermittent pupillary abnormalities occur in some patients. One segment of the iris appears to be pulled into a peak for a brief time and then returns to normal. Thompson, in 1983, reported on 26 patients with these symptoms, 11 of whom had a Horner's syndrome, and summarized the literature.

We describe a 29-year-old white man who came to our neuro-ophthalmic clinic with a history of episodic pupillary distortion brought on by strenuous exercise. We believe this case represents an example of a segmental Horner's syndrome.

Case Report
A 29-year-old, blue-eyed Caucasian man came to our clinic with a 2–3 month history of episodic blurred vision in the right eye brought on when he was lifting weights. The patient reported that his vision would return to normal with cessation of the exercise. Several days prior to our evaluation, the patient had observed his pupils during one of these episodes and found that the right pupil was "distorted." He drew it as an updrawn pupil in the superotemporal quadrant. These episodes were not reported by the patient to be associated with pain, headache, or paresthesia. The patient also reports that his left pupil has been larger than his right pupil since childhood.

On examination, the patient's corrected visual acuity was 20/20 in each eye. The pupillary exam revealed round pupils that measured 4 mm in the right eye and 5 mm in the left eye in semidark conditions; there was no anisocoria in the lighted environment. Direct, consensual, and near pupillary reflexes were normal. The patient's palpebral fissures measured 9 mm and 10 mm, and the near point of accommodation measured 36 cm in the right eye and 27 cm in the left eye. Slit lamp examination was normal without evidence of heterochromia.

During the course of the examination, the patient experienced an episode of right pupillary distortion induced by exercise (Fig. 1). This episode lasted 30–40 s and then the right pupil returned to a normal round configuration (Fig. 2). A 1% Paredrine (hydroxyamphetamine) test was positive (i.e., the involved right pupil dilated poorly, suggesting a partial postganglionic Horner's syndrome). The remainder of the ocular examination and the visual fields were normal.

The patient's workup included blood chemistries, epinephrine blood levels before and after stress, and 24-h urinary VMA, metanephrine, and catecholamine levels, which were all normal. Radiographs of the chest, skull, thoracic spine, and sternum were all normal. The computed tomographic scan of the brain showed prominence of the left cavernous sinus and a slightly slanted sella from right to left (Fig. 3). Digital subtraction angiography of the carotid arteries and cavernous sinuses showed prominence of the left cavernous sinus and a poorly identified right carotid artery.
Because of the poor identification of the right carotid artery, the patient underwent cerebral arteriography, which showed a hypoplastic right internal carotid artery with hypertrophy of several branches of the right external carotid artery.

The right ophthalmic artery was reconstituted by hypertrophy of the posterior ethmoidal branch from the middle meningeal artery, with a normal-appearing choroidal blush in the right eye (Fig. 4).

**Discussion**

We theorize that focal spasm of the iris dilator muscle produced the distorted pupil in the patient described. Sympathetic innervational abnormalities to the dilator muscle are probably the causal factor in our patient, as abnormalities of innervation are often segmental. Thompson feels that the abnormality causing pupillary distortion is of neural origin. He mentioned the possibility that the “peaked segments are supersensitive to catecholamines that reach the muscle via the aqueous” but dismissed it because, in many patients, the pupillary distortions occurred in different segments of the iris with different episodes. However, in our patient, the same segment of the pupil distorted with each episode and it was this very same
Figure 3. Computed tomographic scan of the sellar region in axial plane with contrast enhancement showing considerable asymmetry of the cavernous sinuses, the left side being markedly prominent (asterisk).

Figure 4. A.: Reconstitution of the segmental internal carotid artery via the hypertrophic Vidian artery (large arrows). B: Multiple small collateral channels are still seen at the site of the segmental occlusion of the internal carotid (arrow) in the intermediate phase. C: The left carotid arteriogram shows a cross-filling of the right anterior and middle cerebral arteries via the anterior communicating artery.
area that failed to dilate with hydroxyamphetamine administration. In another argument against the hypersensitivity denervation theory, Thompson reported that his patients did not describe the signs and symptoms usually associated with a sudden increase in levels of circulating catecholamines, i.e., tachycardia, tachypnea, anxiety, and piloerector activity. Interestingly, strenuous exercise was the precipitating factor in our patient's episodes. If the involved segment was truly hypersensitive, it would explain the focal dilation of the pupil with increased levels of circulating catecholamines during strenuous exercise.

We agree with Thompson's statement that a Horner's pupil that does not dilate at all to hydroxyamphetamine is not likely to be supersensitive to aqueous norepinephrine only in a small segment of the iris sphincter. However, our patient does not fit into this category, as his pupils did dilate to hydroxyamphetamine except in the involved segment (Fig. 5).

In summary, we feel that our patient had a segmental postganglionic Horner's syndrome. The damage to part of the sympathetic innervation to the pupillary dilator muscle may have occurred when the right carotid artery suffered its hypoplastic change. We feel that the area of the right pupil that dilates with exercise represents a denervation hypersensitivity response to increased levels of circulating catecholamines.

Acknowledgment

We wish to thank H. Stanley Thompson, M.D., for his critical review of the manuscript.

References

Bilateral Visual Loss in Carotid Artery Disease

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Abstract

Bilateral, simultaneous visual loss usually indicates vertebral-basilar insufficiency. We report the case of a patient who experienced transient, bilateral, simultaneous, asymmetrical visual loss. Arteriography revealed flow-restrictive lesions in both internal carotid arteries. The most likely cause for this symptom is bilateral ophthalmic artery hypoperfusion distal to high-grade stenotic lesions of the internal carotid arteries.

Monocular visual loss is a common symptom of carotid artery disease, whereas bilateral, simultaneous visual loss suggests vertebral-basilar insufficiency. Additionally, bilateral visual loss has been described in association with basilar migraine, raised intracranial pressure with papilledema, cerebral anoxia, meningitis, demyelinating disorders, and following seizures and trauma. We report the case of a patient who experienced transient bilateral simultaneous visual loss in association with severe, bilateral carotid artery disease.

Case Report

A 67-year-old woman was admitted to Los Angeles County-University of Southern California Medical Center for worsening angina pectoris. The patient noted a recent episode of visual loss: She had been sitting quietly when she experienced the abrupt loss of vision in both eyes. She covered each eye individually and judged her vision from the left eye to be totally "black" while vision from her right eye, less severely affected, was described as diffusely "cloudy." This resolved over 2–3 min. The patient denied other neurological symptoms. She had had exertional angina for 4 years but was now experiencing angina at rest, along with orthopnea, paroxysmal nocturnal dyspnea, and pedal edema. She also experienced intermittent calf claudication and had a history of a myocardial infarction, hypertension, and hypercholesterolemia.

The general physical examination revealed a blood pressure of 160/90, and pulse and respiration of 80 and 20, respectively. She was moderately obese. There were bibasilar rales and a grade 2/6 systolic ejection murmur along the left parasternal margin. There was mild pedal edema and pedal pulses were absent. The carotid pulses were normal. There was a left systolic carotid bruit, best heard at the angle of the jaw.

Neurological examination revealed a normal mental status. Cranial nerve evaluation showed visual acuity of 20/16 OD and 20/40 OS, corrected by pinhole. There was pallor of the left optic disc. The pupils were of normal size and light–near dissociation was present bilaterally. There was no afferent pupillary defect. There were no retinal embolic fragments. Visual fields were full to confrontation on repeated testing. The patient exhibited intermittent extinction to a light touch on the left upper extremity. Thenar atrophy, weakness of the abductor pollicis brevis, and Tinel’s sign were present bilaterally. The remainder of the neurological examination was within normal limits.

The laboratory evaluation showed a hematocrit of 37% and a white blood count of 3,900, with a normal differential. The routine blood chemistries were unremarkable. The cholesterol level was 593 mg/dl, triglycerides 106 mg/dl, and sedimentation rate 52. Thyroid function, VDRL, growth hormone, and rheumatoid factor were within normal limits. The chest x-ray film showed borderline cardiomegaly with mild redistribution of flow. The admission ECG showed normal sinus rhythm with nonspecific ST and T wave changes.

Following admission, a myocardial infarction...
was ruled out by normal serial cardiac enzymes. A repeat ECG showed atrial fibrillation with a rapid ventricular response, which was controlled with digoxin. A computerized tomography scan demonstrated an old right subcortical infarct, located in the watershed area between the middle cerebral and posterior cerebral arteries, and communicating with the ventricle. There was no enhancement following infusion of contrast medium. A skull series was normal. The patient then underwent combined cardiac catheterization and cerebral angiography. The cardiac study showed diffuse narrowing of the left anterior descending and right coronary arteries. The aortic arch study revealed a mildly atretic right vertebral artery and a large left vertebral artery, with no definite stenoses. Selective carotid arteriography showed a totally occluded right internal carotid artery just above the bifurcation (Fig. 1) and 60% stenosis of the proximal left internal carotid artery (Fig. 2). No etiology was found for either the carpal tunnel syndromes or the light–near dissociation. The patient was neurologically asymptomatic at follow-up 17 months later.

**Discussion**

Bilateral, simultaneous visual loss due to occipital lobe dysfunction is usually similar in each eye.

The patient discussed here described asymmetrical visual loss that she documented by covering each eye individually. The eye with the greater loss of vision exhibited findings suggestive of optic nerve ischemia, with disc pallor, diminished visual acuity, and absence of homonymous hemianopia. The nature of the patient's ocular signs and symptoms and the presence of profound carotid artery disease all point toward a bilateral anterior circulation, i.e., carotid artery, localization for this patient's visual complaints.

Extracranial arterial occlusive disease may cause symptoms by embolization and/or restriction of flow. The occurrence of bilateral, simultaneous carotid artery emboli would appear to be highly improbable in any patient and even less likely in the present case because of the totally occluded right internal carotid artery. Hemodynamically significant restriction of flow in the internal carotid artery usually requires at least a 50% diameter stenosis, which in this patient was exceeded bilaterally. Focal cerebral ischemia distal to flow-restrictive arterial lesions has been described in hypertensive patients experiencing episodes of hypotension. In the present case, advanced coronary artery disease, with angina, arrhythmias, and congestive heart failure, may have produced a period of diminished cardiac output sufficient to reduce ocular perfusion to ischemic levels bilaterally.

The decision to perform invasive diagnostic procedures in patients with transient ischemic attacks is often based, in part, on the distinction between carotid and vertebral-basilar symptoms. The study of Ueda et al. indicates that this distinction is often imprecise, a finding sup-
ported by the case described here. Bilateral visual loss that is not identical in both eyes may be a presenting symptom of bilateral carotid artery insufficiency.

Acknowledgment

We thank James R. Keane for assistance.

References

Abstract

Sarcoidosis rarely involves the visual system posterior to the chiasm. A 55-year-old woman presented with fluctuating bilateral macular-sparing homonymous hemianopsia. The computed tomographic scan revealed an extensive contrast-enhancing density involving the tentorium, posterior falx, and adjacent medial occipital lobes and cerebellum. Spinal fluid studies revealed a mixed cellular response, and a biopsy of the meninges established the diagnosis of sarcoidosis. Ultimately, vision was lost, despite chronic steroid therapy. The presumed mechanism of visual loss is infiltration of the occipital lobes by meningeal granulomas, possibly with coexistent vascular occlusion.

One-fourth of patients with sarcoidosis have visual involvement, most commonly of ocular origin. Postchiasmal syndromes are rare, and visual field loss due to involvement of the visual cortex has not been reported previously. One such patient, in whom fluctuating cortical visual loss resulted from granulomatous infiltration of the occipital cortex from the adjacent tentorium and falx, is described here.

Case Report

In May 1980, shortly after a minor automobile accident, a 54-year-old woman began having headaches and visual blurring. Her past health had been unremarkable except for mild hypertension of several years’ duration. While hospitalized, she described a loss of all light perception that lasted about 1 h. When vision returned, she was found to have a right homonymous hemianopsia with macular sparing.

The ocular examination was unremarkable. A computed tomographic (CT) scan of the head demonstrated an extensive plaque-like enhancing density involving the tentorium, posterior falx, and adjacent occipital cortex and cerebellum. The ambient and quadrigeminal cisterns were obliterated. Cerebrospinal fluid (CSF) examination revealed 17 white cells with 15% segmented neutrophils, 70% lymphocytes, and 15% large mononuclear cells. The CSF protein level was 56 mg/dL and the glucose level was 59 mg/dL. Cerebral angiography was normal.

No diagnosis was established and the patient did not seek further medical evaluation until February 1981, when she again developed complete loss of vision. Central vision gradually returned. Her corrected visual acuity was 20/20 OU and her ocular examination remained normal. Confrontation visual fields revealed bilateral homonymous hemianopsia with macular sparing. Vision returned, and, when she was hospitalized, Goldmann perimetry demonstrated a complete right homonymous hemianopsia with macular sparing. The left visual field was intact. A chest x-ray film showed symmetrical hilar adenopathy, which had not changed for several years. A CT scan documented persisting enhancement of the tentorium. Some ventricular dilatation had developed since the 1980 scan. The Westergren sedimentation rate was 48 mm/h. The blood count and panel of serum chemistries were normal. The FTA and VDRL were nonreactive. The CSF showed 30 white cells with 10% neutrophils, 62% lymphocytes, and 28% large monocytes. The protein level was 137 mg/dL and the glucose level was 56 mg/dL, with a simultaneous blood glucose level of 123 mg/dL. The CSF cytology and culture results were negative.

A posterior fossa craniotomy revealed granulomatous tissue encasing the tentorium and posterior falx and infiltrating the medial occipital lobes. Pathologic examination confirmed the presence of numerous microgranulomas composed of epithelioid histiocytes and occasional multinucleated Langhan’s giant cells, consistent with sarcoidosis. Cultures of the biopsy specimen for fungi and tuberculosis were negative. A diagnosis of neurosarcoidosis was made and the patient was treated with prednisone, 80 mg/day. After 1 month, the dosage was gradually reduced to 80 mg on alternate days. A repeat
CT scan in September 1981 showed that the ventricles had returned to normal size and the pattern of tentorial enhancement was slightly less pronounced. During this time there was a persistent right homonymous hemianopsia with macular sparing. The patient's maintenance prednisone dosage was 40 mg on alternate days.

In January 1982, the patient experienced the abrupt onset of flashing lights and zigzag lines in her left visual field. These persisted for 2 days and were associated with gradually evolving loss of vision to the left. Goldmann perimetry demonstrated a complete left homonymous hemianopsia, including loss of macular vision. The right homonymous hemianopsia with macular sparing persisted. Thus, vision was limited to 5° to the right of the vertical midline in each eye. External examination again revealed no evidence of ocular sarcoidosis. A repeat CT scan demonstrated persistent enhancement in the region of the tentorium and posterior falx, unchanged from previous examinations (Fig. 1-3). There was no evidence of occipital lobe infarction. CSF examination revealed 2 white cells, a glucose level of 65 mg/dL, and a protein level of 36 mg/dL. The angiotensin-converting enzyme assay was measured for the first time and proved to be normal. Cerebral angiography was normal, with no vascular occlusion or abnormal vascularity in the region of the occipital lobes. The prednisone dosage was increased to 80 mg/day and, over the course of 1 week, there was a gradual return of vision in the left visual field. The prednisone dosage was slowly adjusted to 80 mg on alternate days. Despite continued steroid use, she again lost vision, with preservation of only 5° of central vision bilaterally. In mid-1983, after 1 year without return of vision, she elected to discontinue the prednisone. There has been no change on subsequent clinical examinations and CT scans through April 1984.

Discussion

The central nervous system is affected in 5% of patients with sarcoidosis. While most patients have multisystem disease, some, like the patient described here, have predominantly or exclusively central nervous system involvement.

Most visual symptoms of sarcoidosis derive from ocular disease. Anterior and posterior uveitis, vitreous opacities, perivascular sheathing, and retinal and choroidal exudates may be encountered. The nerve head can be directly involved by a granuloma. Disc edema may result from increased intracranial pressure or as a reaction to the uveitis.

Retrobulbar visual system involvement may result from three basic mechanisms: 1) direct infiltration by the basilar granulomatous meningitis, 2) compression by a granulomatous tumor, and 3) infarction due to angiitis. Visual symptoms might also arise from papilledema or from distortion of the visual system by hydrocephalus due to obstruction of CSF pathways by meningeal granulomas.

The most common neurologic manifestations of sarcoidosis result from the basilar meningitis. Local infiltration into the cranial nerves may produce multiple cranial nerve palsies. Optic nerve and chiasmal damage can result from this mechanism. The optic nerve and chiasm may also be damaged by extrinsic compression from a discrete granulomatous tumor. Byrne and Lawton reported a case of sarcoidosis with visual loss due to papilledema resulting from dural sinus thrombosis. The CT scan showed enhancement of the tentorium and the cerebral angiogram confirmed occlusion of the straight sinus and left lateral sinus. There was no evidence of occipital lobe involvement.

Caplan et al. recently emphasized that basilar meningitis can be associated with a vasculitis, with resulting ischemic damage. Neuro-

Figure 1. Unenhanced horizontal CT scans demonstrating subtle, increased density in the region of the tentorium.
logic involvement in these cases tends to be especially severe. The authors labeled this the angitic form of sarcoidosis and noted that intracocular involvement paralleled the intracranial disease in all cases. They speculated that some of the transient symptoms encountered in neurosarcoidosis may have a vascular mechanism.

Homonymous visual field loss because of damage to the postchiasmal visual radiation has been a rare occurrence in sarcoidosis. Everts described a patient with a right homonymous hemianopsia owing to a left occipital lobe granulomatous tumor. The present case is unique, since occipital lobe involvement resulted from direct infiltration of the granulomatous tissue associated with the basilar meningitis. The meningeal reaction extended to the tentorium and adjacent falx. Involvement of these structures provided the framework for extension into the occipital lobes.

Our patient's course was characterized by dramatic fluctuations in visual field involvement. The early fluctuations occurred before steroid therapy, demonstrating that spontaneous improvement is possible. While corticosteroids remain the drugs of choice, improvement may be incomplete or transient. Most patients with sarcoid meningitis continue to deteriorate despite steroid therapy. Given the potential for spontaneous improvement, an apparent response to therapy must be interpreted with some caution. Ultimately, our patient sustained severe loss of vision, with bilateral homonymous hemianopsia with macular sparing. Her symptoms and the CT abnormalities have not changed despite cessation of steroid

![Figure 2. Horizontal CT scans showing a contrast-enhancing density involving and adjacent to the tentorium.](image)

![Figure 3. Coronal CT scans demonstrating the contrast-enhancing density in the region of the tentorium and posterior falx.](image)
therapy. Clearly, alternatives to steroid therapy are desirable. Recently, low-dose, whole-brain irradiation has been suggested.\(^1\)

The fluctuating visual symptoms in the present case suggest a possible vascular mechanism, consistent with the angiitic process proposed by Caplan et al.\(^8\) Unlike their cases, our patient never demonstrated ocular sarcoidosis. Two angiograms failed to show evidence of vascular involvement. Pathological examination may be required to document the presence of angiitis. Indeed, the existence of a discrete angiitic form of sarcoidosis is questionable, since all cases so classified have had active basilar meningitis. The vascular involvement may simply reflect the local inflammatory effect of the meningitis and may have a mechanism similar to the vasculitis that is encountered in other forms of acute and chronic meningitis. Igarashi et al.\(^11\) speculated that the vascular occlusions occurring in acute meningitis result from vasospasm, with a mechanism similar to that encountered in subarachnoid hemorrhage. Thus, damage to structures adjacent to the granulomatous meningitis may result from the combination of local granulomatous infiltration and inflammatory vascular occlusion.

Although a rare cause of postchiasmal visual loss, sarcoidosis must be considered when a homonymous hemianopsia is associated with a pattern of chronic meningitis. Evaluation of unexplained chronic, fluctuating visual loss should include a CSF examination. The discovery of pleocytosis, or abnormal CT enhancement in the region of the tentorium indicates the presence of a local inflammatory process, requiring consideration of neurosarcoidosis.

Acknowledgment

James Corbett, M.D., critically reviewed the manuscript.

References

Malignant Fibrous Histiocytoma of the Orbit

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Abstract
A recent review of orbital tumors at the Armed Forces Institute of Pathology has shown that fibrous histiocytoma is the most common primary mesenchymal tumor of the orbit in adults. This surprising statistic is explained by the fact that the histologic classification of mesenchymal neoplasms has been revised extensively during the last two decades to include previously distinct tumors of fibrous tissue under the common histopathologic diagnosis of fibrous histiocytoma. We present the computed tomographic findings of a primary malignant fibrous histiocytoma of the orbit, along with a review of the literature.

Since the early 1960s, the term fibrous histiocytoma has encompassed various mesenchymal tumors that were previously considered separate pathologic entities. The International Histologic Classification of Tumors currently includes under fibrous histiocytoma the following entities: dermatofibroma, sclerosing hemangioma, nodular tenosynovitis or giant cell tumor of the tendon sheath, pigmented villonodular synovitis, atypical fibrous histiocytoma, dermatofibrosarcoma protuberans, fibroxanthosarcoma, xanthogranuloma, and malignant giant cell tumors of the soft tissues (Table 1).

All of these benign and malignant lesions possess, as a common denominator, variable proportions of fibroblastic and histiocytic cells that are arranged in fascicles with a characteristic "storiform" pattern. The orbit appears to be a site of predilection for fibrohistiocytic lesions, and several cases have been reported as well as a series of 150 cases reviewed at the Armed Forces Institute of Pathology (AFIP).

In spite of the increasing interest in malignant fibrous histiocytoma, the radiologic findings, particularly by computed tomography, of this neoplasm in the orbit have not been reported. The clinical, radiologic, and pathologic findings of a case of malignant fibrous histiocytoma are presented here, along with a review of the literature.

Case Report
The patient was a 44-year-old man with a history of slowly progressive loss of vision in the central field of the right eye associated with pain. The patient was otherwise healthy.

Neuro-ophthalmological evaluation revealed a visual acuity of 20/25+2 in the right eye and 20/20 in the left eye. An afferent pupillary defect was present on the right. The patient missed 5/15 American Optical color plates with the right eye and only 1/15 with the left. There was limitation of upward gaze on the right with a restriction of forced ductions. Goldmann visual fields demonstrated a superior, paracentral scotoma in the right eye. Ophthalmoscopy revealed mild blurring of the right disc margins. Four millimeters of proptosis could be detected with Krahn exophthalmometry on the right side.

Computed tomography was performed. A mass of soft tissue density was detected in the right orbital apex within the muscle cone. The mass extended through the superior orbital fissure into the cavernous sinus (Figs. 1a and b).

Therapy with 80 mg prednisone daily was administered during a 4-day trial. The patient noticed subjective improvement of the orbital pain but worsening of the vision. The visual acuity dropped to 20/30+2 in the right eye. The limi-
tation of upward gaze persisted and opthalmoscopy revealed frank papilledema with formation of concentric chorioretinal folds as described by Paton in the peripapillary region.

The trial of steroids was deemed unsuccessful and surgical exploration and biopsy were recommended. The orbit was approached through a modified Kronlein incision. A white, compressible tumor mass was seen and palpated in the posterior aspect of the orbit within the muscle cone. The tumor was firmly attached to the orbital apex so that complete extirpation was not possible. The tumor was debulked and submitted for pathologic examination. Frozen sections of the tumor were diagnosed as fibroxanthoma; however, review of the permanent sections demonstrated the spindle-shaped cells arranged in fascicles typical of fibrous histiocytoma. Postoperatively, the patient did well. The vision in the right eye improved to 20/10 – 2.

Discussion

Font and Hidayat reviewed 150 cases of fibrous histiocytoma of the orbit submitted to the AFIP and concluded that it is the most common mesenchymal tumor of the orbit in adults. Fibrous histiocytoma is a mesenchymal tumor that frequently involves the skeletal muscle, fascia, and adipose tissue. However, its predilection for the orbit is not widely recognized. In fact, it is more common than cavernous hemangiomas, Schwannomas, or meningiomas of the orbit. The concept of fibrohistiocytic tumors is derived from the questionable assumptions that histiocytes may act as facultative fibroblasts and that primitive mesenchymal elements may give rise to both fibroblasts and histiocytes. However, Kojima presented histochemical evidence that some histiocytes are activated forms of fibroblasts, thus lending support to the hypothesis of fibrohistiocytic neoplasms.

Fibrous histiocytomas of the orbit usually appear in the fifth or sixth decade of life and do not have any predilection for sex or race. The most common signs and symptoms of the tumor are proptosis, palpable mass, decreased vision, and pain. Visual field defects and signs of optic nerve compression are also frequent. The tumor can also present as an external ophthalmoplegia.

Histopathologically, the tumor is classified as benign, locally aggressive, or malignant on the basis of its biologic behavior. Representative illustrations from cases unrelated to the one described here depict the storiform pattern of fibroblasts and histiocytes without atypia seen in the benign form (Fig. 2) and the pleomorphism and giant cells typical of the malignant fibrous histiocytoma (Fig. 3). Primary orbital malignant fibrous histiocytoma is the least frequent form, accounting for only 17 of the 150 cases reviewed at the AFIP. Malignant fibrous histiocytomas of the orbit are usually larger at the time of initial examination than the benign and locally aggressive ones. The symptoms are usually acute rather than chronic, complete surgical removal is often difficult, and the recurrence rate is very high. Overall, the prognosis for the malignant variant of the tumor is very poor, due to its high recurrence rate, its radioresistance, and widespread metastases.

The radiologic method of choice for evaluation of malignant fibrous histiocytoma is computed tomography. Its appearance in the orbit is similar to that of fibrohistiocytic tumors in other locations, usually presenting as masses of muscle density with possible central areas of decreased absorption values representing central necrosis. Computed tomography can also demonstrate bony erosions, muscle or nerve infiltration, and extension into surrounding structures such as the cavernous sinus.

Although some malignant fibrous histiocytomas may contain, on histologic examination, lipid-filled vacuoles within the cytoplasm of the cells, fat is not detectable by computed tomography. This is a very useful differential feature that allows distinction of fibrous histiocytomas from other mesenchymal tumors of the orbit such as lipomas and liposarcomas, in which lucent areas representing fat are commonly present.

Other alternative imaging modalities can be

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<th>TABLE 1. Synonyms of Fibrous Histiocytoma</th>
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<td>Subepidermal nodular fibrosis</td>
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<td>Dermatofibroma</td>
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<td>Sclerosing hemangioma</td>
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<td>Progressive recurrent dermatofibroma</td>
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<td>Xanthogranuloma</td>
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<td>Fibrous xanthosarcoma</td>
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<td>Juvenile xanthogranuloma</td>
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<td>Atypical fibrous histiocytoma</td>
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<td>Atypical fibroxanthoma</td>
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<td>Nodular tenosynovitis</td>
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<td>Pigmented nodular tenosynovitis</td>
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<td>Giant cell tumor of soft tissues and tendons</td>
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<td>Nevus histiocytoma</td>
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<td>Nevocanthomendothelioma</td>
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<td>Reticulocyctic granuloma</td>
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<td>Dermatofibrosarcoma protuberans</td>
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<td>Epithelioid sarcoma</td>
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Data from ref. 2.
Figure 1. a: A plain, axial computed tomographic scan demonstrates a soft tissue mass (arrow) in the right orbital apex contiguous with and located superior and lateral to the optic nerve within the muscle cone. b: A repeat, axial scan after the intravenous administration of 100 ml (40 g) of iodinated contrast agent demonstrates ring enhancement with extension of the mass through the superior orbital tissue (arrow) into the middle cranial fossa contiguous with the cavernous sinus.
used in malignant fibrous histiocytoma of the orbit, such as scintigraphy, angiography, and ultrasonography. The diagnostic information that can be obtained by computed tomography is far superior to any other modality, in our opinion.12

The radiological differential diagnosis of orbital malignant fibrohistiocytoma should include neurofibromatosis, neurilemoma, hemangiopericytoma, nodular fascitis, rhabdomyosarcoma, lymphoma, hemangioma, melanoma, and metastasis.10,11

Acknowledgment

We appreciate the collaboration of Dr. A. A. Haydavatt of the Ophthalmic Pathology Branch, AFIP, for providing the microscopic illustrations that appear in this article. We extend our appreciation also to Dr. J. Lawton Smith for his encouragement and guidance.

References

Isolated Facial Myokymia and Facial Contracture: Computed Tomography and Magnetic Resonance Imaging Correlation

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Abstract
Isolated facial myokymia with contracture can be the earliest manifestation of intrinsic lesions of the brainstem. We report a case of facial myokymia with contracture occurring as the result of a pontine glioma, as depicted on cranial computed tomography and magnetic resonance imaging studies. The rostral location of the tumor supports the supranuclear disinhibition hypothesis of facial myokymia.

Facial myokymia is a condition of continuous, fine, undulating movements of the face caused by spontaneous contraction of one or more facial muscles. If restricted to the eyelids, myokymia may be considered a benign condition. However, more generalized facial involvement, especially if facial contracture is also present, suggests demonstrable brainstem pathology. Although the pathophysiologic mechanism underlying facial myokymia is unknown, supranuclear disinhibition of the facial nucleus has been hypothesized. We report a case of facial myokymia with contracture and computed tomography (CT) and magnetic resonance imaging (MRI) evidence of tumor involvement in the brainstem rostral to the facial nucleus, thus supporting the hypothesis of supranuclear facial disinhibition.

Case Report
A 26-year-old woman complained of continuous, painless "twitching" of her right eyelid and mouth for about 4–6 weeks. This was appreciated by others more readily than by herself. Aside from occasional headaches, she had no history of the same or other neurological problems. The physical examination was unremarkable except for persistent myokymia of the right orbicularis oculi, buccinator, orbicularis oris, mentalis, and platysma. The right palpebral fissure was narrowed and the right nasolabial fold deepened. Facial sensation and strength were intact. Corneal, sneezing, and masseter reflexes were preserved. The remainder of the general neurological and physical examination was normal.

Electromyography revealed numerous iterative discharges of the orbicularis oris lasting 1.5–1.75 s. Each discharge was produced by single motor units firing either individually or in conjunction with another motor unit. The firing rate was 36–63/Hz against a rather steady background firing at 20 Hz. Occasionally, there were progressive changes in interval (and more rarely in frequency), producing a sound reminiscent of myotonic discharges. Electrically elicited blink reflex revealed an absent R1 (early) component on the right, and normal R2 (late) component bilaterally.

Visual evoked, somatosensory, and brainstem auditory evoked potentials were normal. Cranial CT showed a low-density area on the right side of the upper pons extending super-
iorly toward the right cerebral peduncle, with obliteration of the right side of the ambient cistern (Fig. 1). MRI was done in the transverse axial plane and midsagittal plane, through the posterior fossa. A spin echo image (Fig. 2a) demonstrated focal expansion of the superior portion of the right cerebral peduncle and upper pons by a low-intensity (dark) mass. Spin echo and inversion recovery images (Fig. 2b and 2c) showed exophytic extension of the mass within the right ambient cistern. The remainder of the brainstem, including the lower pons, was normal. The image characteristics were consistent with the prolonged T1 and T2 often seen in cases of brainstem neoplasia.

Four-vessel cerebral angiography was unremarkable. The patient underwent focal radiation therapy to the mass, receiving 5,580 rad in 31 fractions (180 rad each) over a 43-day period (7.5 × 6.0 cm port, 10 MeV photon source). She has been stable after 6 months, except for development of a mild facial paresis, evident on attempted movement of the face. The tonic contracture and myokymia are unchanged.

Discussion

Following the description of Bernardt\(^1\) in 1902, the finding of facial myokymia subse-

![Figure 1. Area of lucency (arrows) in the right side of the upper brainstem causing obliteration of the right ambient cistern and deformity of the fourth ventricle. After infusion of contrast, no enhancement was detected.](Image)

quently was considered pathognomonic for multiple sclerosis. Several cases due to brainstem tumors have since been reported. In 43 cases of facial myokymia, 42\% were associated with multiple sclerosis and 14\% with brainstem or posterior fossa tumors. The remaining 44\% included cases of verteobasilar ischemia, polyradiculoneuropathy, hemifacial spasm, peripheral facial paralysis, trigeminal neuralgia, syringobulbia, abortive Little’s disease, phosgene poisoning, and amyotrophic lateral sclerosis.

As a manifestation of multiple sclerosis, facial myokymia usually occurs transiently, lasting from days to months, and may present alternatingly but on different occasions on either side of the face. Nuclear or supranuclear facial weakness often coexists but is mild. On electromyography, spontaneous, rhythmic, motor unit discharges are commonly continuous but asynchronous between adjacent facial muscles.\(^1\)

In the case of brainstem tumors, facial myokymia is typically unilateral and of longer duration, until it is replaced by a more severe and progressive facial palsy. Discontinuous motor unit bursts are found on electromyography, as in our case. Tumor size does not correlate well with the extent of facial musculature involved by myokymia.\(^1\) In the rare instance when myokymia involves several cranial nerves, the tumor has substantial rostral-caudal involvement of the brainstem.\(^4\)

Various mechanisms have been proposed to explain tumor-related facial myokymia. One hypothesis concerns the loss of interneurons that synapse on neurons of the facial nucleus. Loss of such inhibitory or dampening influences would allow the nonreflexic, high neuronal firing rate to occur, as seen on electromyography.\(^5\) The second hypothesis suggests disinhibition of the facial nucleus by loss of more rostral supranuclear, especially corticobulbar, pathways.

The radiologic findings in our case favor the latter hypothesis. Tumor localization to the upper pons and midbrain would interrupt the corticobulbar pathways to the facial nucleus, sparing the nucleus itself or adjacent interneurons.

Though autopsy material is rare, two patients with facial myokymia had rostral brainstem lesions with sparing of the facial nucleus, supporting the hypothesis of supranuclear disinhibition.\(^2\)\(^3\) A third case was very similar, but edema and gliosis of the facial nucleus complicate the interpretation.\(^7\)

Only one or two previous cases of brainstem tumor apparently presented solely with facial
myokymia and contracture, without paresis. A mild facial paresis may evolve later, as in our patient. Occasionally, facial paresis and tonic contracture coexist without myokymia in cases of brainstem glioma.

Our case report is most intriguing because of the paucity of neurological signs in spite of extensive tumor involvement of the upper pons and cerebral peduncle, as shown by CT and MRI. The paucity of neurological findings, belies the extensive tumor infiltration of brainstem tracts prior to neuronal destruction.
Acknowledgment

The authors wish to thank Marcy Young and Lisa Gustafson for their assistance in manuscript preparation.

References

Association of Bilateral Internuclear Ophthalmoplegia and Myelomeningocele with Arnold–Chiari Malformation, Type II

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Abstract
We describe the unusual association of long-standing repaired myelomeningocele, hydrocephalus, and Arnold–Chiari malformation with bilateral internuclear ophthalmoplegia in a young man. A rarely reported association, this case emphasizes the need for further neuroradiologic evaluation to determine the possibility of third-ventricle enlargement with worsening hydrocephalus.

Myelomeningoceles are frequently associated with the Arnold–Chiari malformation. This central nervous system malformation may vary in anatomical and clinical severity. Arnold–Chiari malformation, Type II, the most common form, consists of pontine, medullary, and cerebellar distortion and protrusion into the spinal cord. It is nearly always associated with myelomeningoceles. In addition to the other brainstem anomalies, the aqueduct of Sylvius may be obstructed in this malformation, leading to hydrocephalus with distention of the lateral and third ventricles.

Bilateral internuclear ophthalmoplegia is a disorder of oculomotor function in which conjugate horizontal gaze is impaired secondary to brainstem lesions involving the medial longitudinal fasciculus. Such brainstem pathology is frequently seen in adult patients with neurological disease. We report the unusual association of a long-standing surgically repaired myelomeningocele and Arnold–Chiari malformation.

Case Report
The patient is now a 20-year-old white man. He was born with a large lumbar myelomeningocele that was surgically repaired shortly after birth. Following surgery, the patient demonstrated a flaccid paraparesis, a neurogenic bladder, and an L-4 sensory level. At about 15 years of age, he began complaining of mild bifrontal headaches and his family first noted that at times his eyes “jiggled.” He was examined by a neurologist who confirmed the diagnosis of bilateral internuclear ophthalmoplegia. No further evaluation was performed. Over the next 5 years, his headaches worsened, and he and his family continued to note disconjugate eye movements and nystagmus on horizontal versions.

On recent examination, the patient’s muscular development in the upper extremities was good, but his lower extremities were flaccid and atrophic. The head circumference was 59 cm (95%). The mental status examination was normal. Visual acuity was 20/20 in each eye. Funduscopically revealed mild, chronic disc edema bilaterally. Confrontational visual field testing was normal. A motility examination revealed that, on lateral gaze, a clear-cut bilateral internuclear ophthalmoplegia was present, with paresis of the adducting eye and nystagmoid movements of the abducting eye. Upward gaze was slightly limited and vertical nystagmus was present; downward gaze was also slightly limited. There was a small A-pattern intermittent exotropia evident, measuring 10 prism diopters in primary, 20 prism diopters in downward gaze, and 5 prism diopters in upward gaze. Convergence was normal. Pupillary size and reactivity to light and accommodation were normal. Lower cranial nerve function was...
normal. The remainder of the neurologic examination confirmed an L-4 sensory and motor level consistent with the surgical findings at the time of myelomeningocele closure.

Computerized tomographic scans of the brain revealed massive dilatation of the lateral and third ventricles with no enlargement of the fourth ventricle, suggesting an obstructive hydrocephalus at the level of the aqueduct of Sylvius (Fig. 1). The frontal horns of the lateral ventricles had a configuration typical of Arnold-Chiari malformation. The patient underwent surgery for a ventriculoperitoneal shunt through the right lateral ventricle and had an uneventful postoperative course with gradual resolution of the headaches. After 2 months, reexamination revealed that the internuclear ophthalmoplegia was unchanged. Computerized tomographic scans demonstrated significant improvement in ventricular size (Figs. 2 and 3).

Discussion

Naidich et al.\textsuperscript{2} recently reviewed the mesencephalic neuroanatomy and neuroradiology of the Arnold-Chiari Type II malformation. The simultaneous occurrence of the Arnold-Chiari malformation and bilateral internuclear ophthalmoplegia has rarely been reported. Cogan,\textsuperscript{3} listing various causes of internuclear ophthalmoplegia, described two patients with Arnold-Chiari malformation. One of these patients was an 8-year-old boy. Houtman\textsuperscript{4} also noted one case. Other reviews of the neuro-ophthalmologic findings in Arnold-Chiari malformation

![Figure 1. Computerized tomographic scan of brain before ventriculoperitoneal shunt.](image1)

![Figure 2. Computerized tomographic scan of brain after shunt.](image2)

![Figure 3. Computerized tomographic scan of mesencephalon after shunt.](image3)
reported no confirmed internuclear ophthalmoplegia.\textsuperscript{5, 6} Well-described causes of bilateral or unilateral internuclear ophthalmoplegia include multiple sclerosis, infiltrative tumors, neurosyphilis, and arteriosclerotic or inflammatory vascular disease. Occasionally, myasthenia gravis may have a neuro-ophthalmologic finding suggestive of internuclear ophthalmoplegia. All of these disorders are uncommon in the pediatric patient, while the Arnold-Chiari malformation and hydrocephalus are seen quite often.

Clinically, internuclear ophthalmoplegia consists of a characteristic syndrome of paresis of adduction of one eye and horizontal nystagmus of the contralateral abducting eye on attempted versions to the left or right or both. Convergence and light reflexes generally are well preserved. Upward gaze is associated with vertical nystagmus. Subjective visual complaints by the patient are few, if any, in long-standing cases of internuclear ophthalmoplegia.

Internuclear ophthalmoplegia clearly can be localized to lesions of the medial longitudinal fasciculus. This tract is an associative fiber system running throughout the brainstem ventromedially to the aqueduct of Sylvius and extending into the cervical spinal cord. The medial longitudinal fasciculus receives input from the vestibular and other proprioceptive systems and coordinates this input with the oculomotor and abducens motor complexes, thus permitting conjugate horizontal eye movements.

Our patient also demonstrated an A-pattern exotropia. This is a well-recognized condition associated with spina bifida and myelomeningocele.\textsuperscript{11-13} Its occurrence is probably independent of the diagnostic findings present in internuclear ophthalmoplegia.

The case described here points out that bilateral internuclear ophthalmoplegia may be a presenting feature of the Arnold-Chiari malformation associated with hydrocephalus in pediatric myelomeningocele patients. The pathophysiologic cause of internuclear ophthalmoplegia in our patient may be the disruption of the medial longitudinal fasciculus owing to brainstem distortion or the presence of primary embryologic malformations of this tract. The internuclear ophthalmoplegia, however, may signal compression of the medial longitudinal fasciculus by third-ventricle enlargement, indicating worsening hydrocephalus, which would require further neurroradiologic evaluation and surgical therapy. However, in long-standing hydrocephalus such as in this case, shunting may not relieve the internuclear ophthalmoplegia.

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Cysticercosis

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"Cysticercosis reveals in the World as a notable coincidence with the dark zones of poverty and social unequality although no social class or ethnic group is free of suffering it."

L. J. Damonte-Vicillo

Cysticerci are probably a degenerated form of the larvae of Taenia solium. The larvae are acquired by humans, who act as the intermediate host after ingesting the eggs of the taenia. A brief review of the biologic cycle of *T. solium* is pertinent for the proper understanding of the natural history of cysticercosis.

Taeniasis is an infestation of humans, who act as a definitive host; it is acquired after the ingestion of insufficiently cooked pork meat contaminated with the larvae of *Cysticercus cellulose*.

In the human small bowel the larva develops into the adult tapeworm, which may attain a length of 1–8 m. The scolex (or head) of the cestode attaches to the intestinal mucosa and starts to form multiple segments called proglottids. Each proglottid, after fecundation, carries thousands of ova that are excreted in the human feces. Swine, acting as an intermediate host, ingest the eggs of the parasite that later develop into the larvae of *C. cellulose*, thus completing the cycle. Any individual may acquire cysticercosis and act as intermediate hosts by external autoinfection, e.g., ingesting eggs contained in contaminated water or food, especially raw vegetables and some fruits. Other ways to get the disease are autoinfection via anus-hand-mouth contact in persons who harbor the adult parasite and who exercise poor hygiene. A form of internal autoinfection has been suggested in which mature proglottids are regurgitated into the stomach, liberating the eggs by enzymatic activity; however, this has not yet been proven. After the ingestion of the eggs, the action of bile and digestive enzymes liberates and activates embryos that bear hooks; they are called oncospheres and were protected previously by a thick shell. These embryos invade the intestinal wall, enter the circulatory system, and are transported to various tissues where they form the vesicles of cysticerci.

Muscle and brain are the main targets because of their high glucose and glycogen contents and the rich vascular net, which also explains the embryos' predominant location in the gray matter, subarachnoid space, and ventricular system. The eye and spine are other important targets. The parasite may be present in two forms. The most frequent, *C. cellulose*, has a characteristic scolex. The other form is *C. racemose*, which lacks a scolex, is larger, and shows a tendency to predominate in the subarachnoid space. It probably represents a degenerative form of *C. cellulose*.

Human cysticercosis is the most frequent parasite caused disease in the world affecting the central nervous system (CNS). Although it has been found frequently in developing countries, with recent massive immigration, more cases have been found in the southwest United States and other countries. In Latin America, the disease is particularly frequent, especially in Mexico.

Based on an autopsy series from Mexico, it was concluded that 3 of 100 individuals suffer from the disease and that in 1 of 100 the parasite is the cause of death. Additional data, mainly from Mexico, include the following:

1. The disease is the third most frequent cause of admission (excluding psychiatric disorders) in neurological wards.

2. The brain is involved in 60–92% of patients with cysticercosis, and 17–25% of patients with cerebral cysticercosis had simultaneous infestation with taeniasis.

3. In neurological interventions over a period of 5 years, 28.2% were motivated by neurological symptoms secondary to cerebral cysticercosis.

4. Cysticercosis was found in 25% of craniotomies performed on the basis of the clinical diagnosis of brain mass (before the advent of computed tomography).
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5. Cysticercosis is found in 25% of patients with increased intracranial pressure.11

6. Death occurs in 1 of every 5 patients with CNS cysticercosis.15

7. In some countries, the disease is considered the most frequent nonneoplastic, space-occupying lesion intracranially and a major cause of disability.16

8. In a review of 135 autopsy cases, Rabiela et al.15 concluded that in 80% the finding of cysticercosis was incidental, without clinical symptoms, and in 20% the parasitosis caused symptoms or death. This conclusion would indicate, in theory, the possibility of some kind of immunologically mediated relationship between host and parasite that determines the aggressiveness of the disease. Based on this idea, Estanol17 proposed several types of cerebral cysticercosis in humans, including: (a) cerebral infestation without disease; (b) cerebral infestation with benign disease that resolves spontaneously with calcifications of the parasite; this type could produce sequelae, mainly in the form of an irritative area that causes seizures;18 (c) cerebral infestation with progressive disease, with inflammatory reaction in the form of arachnoiditis, vasculitis, and multiple granulomatous or cystic lesions in any compartment of the brain.

The mechanisms of production of cerebral lesion in cysticercosis include17 (a) mechanical, with obstruction of free pathways of cerebrospinal fluid (CSF) and mass effect; and (b) inflammatory, with arachnoiditis, vasculitis and ischemia, multiple granuloma, and edema. The mechanisms that produce symptoms are cortical irritation, cerebral compression, tissue destruction, and intracranial hypertension.17

The severity of cerebral lesions is related to the number and location of the cysts or granulomas, the degree of mass effect or surrounding edema, extension of the process, time of exposure, vascular and inflammatory activity, glial scarring, obstruction within the ventricular system, and basal arachnoiditis with impairment of CSF circulation.10

Neurocysticercosis may mimic any neurologic disorder.6-7,10,14-21 It may present with minimal or a wide variety of symptoms and signs, which may improve or worsen spontaneously and rapidly. In multiple lesions in the brain parenchyma or involvement with mixed disease in different compartments, the clinical expression of the disease may be the combination of the findings in the affected areas. The eye, usually via the ophthalmic artery, is affected in less than 2% of cysticercosis cases. Cysticerci can be carried to any part of the orbit and globe.19,22,23 Both eyes are infrequently affected simultaneously, and it is rare that one eye is involved by multiple cysticerci. The most common implantation site is under the retina over the macular area (67.5–90.5%), and total retinal detachment can occur.23 The parasite can migrate through the hyaloid membrane to become free in the vitreous. The death of the parasite may be associated with a marked immunologic reaction, with acute swelling leading to uveitis and, rarely, atrophy or even sudden blindness.23

The clinical diagnosis of intraocular cysticercosis is not difficult if the parasite is alive, but if the parasite dies its disintegration causes disorganization of intraocular structures, making the proper diagnosis almost impossible.22

The laboratory tests used in the diagnosis of suspected neurocysticercosis are several. The

Figure 1. Acute focal encephalitic phase of cysticercosis in a 3-year-old girl. a: Noncontrast-enhanced CT scan shows a hypodense area in the occipital region in relation to edema. b: Contrast-enhanced CT scan shows the cysticercus vesicle as a thick ring of enhancement with central fluid density, peripherally placed in the area of edema.
CSF examination results may be normal or the findings may include pleocytosis with a predominance of lymphocytes, eosinophilia, and an increase in total proteins, mainly gammaglobulins. The glucose content can be normal or low; this finding could be related to a severe process.1,6,7,10

The Nieto complement fixation test21,25 has been used widely, with an accuracy of 80–97% when performed in the spinal fluid during the active phase of the disease; this test might have a negative result in cases of parenchymal cysticercosis when the vesicles are not in contact with the subarachnoid space. There also may be cross-reactions with other cestodes and treponemases.4

Another, more recent test is an indirect hemagglutination test26 in which serum titers of 1:64 or more are positive in 87% of cysticercosis cases. This test may also show false-positive results due to cross-reactions with Echinococcus and other cestodes.4

Electroencephalographic recordings may show abnormal, although nonspecific, findings in patients with proven cysticercosis.8,9

A short description of the pathological changes that occur with parasite infestation is necessary before the computed tomography (CT) findings are reviewed.

Cysticercosis show several stages of evolution.1,2 The earliest is the vesicular stage, in which the inflammatory reaction and edema predominate, along with capillary network proliferation and the formation of a connective
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The tissue capsule around the vesicle with fluid. The overall picture is similar to that of any granulomatous reaction. The next is the colloidal stage, in which the inflammatory reaction diminishes and the fluid is replaced by a jelly-like material secondary to hyaline degeneration. In the granular nodular stage, the cyst reduces in size and mineralization starts. The last stage is the calcified nodule. It is believed that cysticerci live an average of 2–5 years before they reach this last stage. In the meningeal and intraventricular localization of the parasite, all the different stages can be found, but the inflammatory reaction can be worse and persist longer, producing arachnoiditis or ependymitis that can lead to fibrosis and obstruction. These latter forms can also produce vasculitis to a variable degree.

CT is the most reliable and sensitive method of evaluating patients who have this disease. It has provided much information about the natural history of the disease. The diagnostic accuracy of the method has been reported to be as high as 97%. In a review of 10,000 CT scans done over a period of 5 years, some form of cysticercosis was found in 20.4%. In another series of 10,895 CT examinations done over a similar period, 1.107 cases demonstrated findings compatible with intracranial cysticercosis. This entity has been classified by CT results according to the areas of involvement, i.e., parenchymal, meningeal, intraventricular, and mixed forms.

Parenchymal Form

The parenchymal type is the most frequent. It is widely divided into two forms: an acute encephalitic phase and a nonencephalitic phase, which can be either acute or chronic.
The earliest and most frequent presentation found in children and young adults is the acute encephalitic phase. The unenhanced CT scan shows a single area of low parenchymal density in relation to focal edema, usually in the subcortical white matter, without ventricular compression. Clinically, the patient presents without intracranial hypertension. In the same phase, other presentations include diffuse or multiple areas of irregular low density, representing edema, that accentuate the appearance of white matter mainly at the region of the centrum ovale. There is a symmetrical decrease in the size of the ventricles and, clinically, intracranial hypertension may be found. The contrast-enhanced scan shows a single 5–15 mm, well-defined, ring-like lesion adjacent to the area of edema, or multiple, diffusely distributed annular lesions with similar characteristics. The ring of enhancement is explained by an increase in vascularity, with capillary proliferation adjacent to the vesicles. A single focal lesion is seen in approximately 15% of cases and multiple ones in 85%. This acute phase usually lasts 2–6 months and varies in intensity and duration with each individual. The ring of enhancement persists through the acute phase, and edema subsides more rapidly in single lesions and lasts longer in the multiple form. It may persist after the vesicles have become isodense with the brain parenchyma. The ventricles return to normal size as soon as the edema starts to subside.

If the disease does not worsen, there is a good correlation between clinical improvement and the progressive disappearance of the lesions. There seems to be a mortality of about 10% in the acute phase, despite appropriate treatment. Follow-up examination may show a
normal appearance of the brain or a wide spectrum of findings, ranging from parenchymal focal abnormalities and/or hydrocephalus to residual small, single or multiple calcifications (Fig. 2c and 2f). These multiple parenchymal calcifications have been called the miliary form (Fig. 16c). This type of calcification is seen in only 30% of skull radiographs. An unusual presentation of the acute encephalitic phase is normal-appearing brain parenchyma with small ventricles and no ring-like lesions present, an image similar to findings of pseudotumor cerebri.[2]

The nonencephalitic phase of parenchymal cysticercosis may show well-defined, regular cystic lesions, varying in size from a few millimeters to several centimeters (Fig. 4b and 4c). Some of the small cystic lesions show a small, eccentric density within the lumen that represents the invaginated scolex of the cysticerci (Fig. 4d). The contrast-enhanced scan demonstrates better definition of the lesions due to

Figure 5. Parenchymal cysticercosis with different stages of evolution in the same examination of a 48-year-old woman. a: Noncontrast-enhanced CT scan shows several small calcified cysticerci in the left hemisphere. b: Contrast-enhanced CT scan shows two ring lesions with minimal perilesional edema located in the right temporal region. Two cystic lesions without peripheral enhancement or edema are seen in the left hemisphere. c: A mixture of calcifications, vesicles, and nodules are seen in the last image scan.

Figure 6. Parenchymal cysticercosis, calcified stage. Noncontrast-enhanced CT scan shows multiple small calcifications in both cerebral hemispheres. Note the tendency of many lesions to be located close to the subarachnoid space. The largest calcification in the midline is physiologic and related to the falx.
Figure 7. Meningeal form of cysticercosis. a: Noncontrast-enhanced CT scan shows multiple cystic lesions at the base of the brain in the subarachnoid space, with some calcifications at the right Sylvian fissure. The temporal horns are prominent. b: Another patient with similar findings. In the contrast-enhanced CT scan no ring enhancement is evident. A small cyst is seen adjacent to the left middle cerebral artery. There is curvilinear calcification between the two cysts in the right Sylvian fissure.

Figure 8. Cysticercosis, meningeal form, racemose variety. a: Conglomerate of cystic lesions in the left temporo-parietal region without ring enhancement, and compression of brain parenchyma and left ventricle. Small calcifications between cysts are evident. b: Another patient with multinodulated cystic lesions at the left temporal lobe, detorming the subarachnoid space and Sylvian fissure.

Not infrequently, the examination shows cysts of different sizes that have variable responses to contrast material, in addition to isolated focal edema and some calcifications, which indicate different stages in the evolution of the parasite². Solitary cystic lesions are unusual and must be differentiated from other cyst-like lesions and neoplasms such as hydatid cyst, tuberculosis, abscess, and cystic astrocytoma. The cystic nonencephalitic form of parenchymal dis-
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Figure 9. Meningeal form of cysticercosis with basal arachnoiditis. a: Noncontrast-enhanced CT scan shows obliteration of the basal cisterns and Sylvian fissures, with an image isodense to the brain parenchyma. b: Contrast-enhanced CT scan shows diffuse leptomeningeal enhancement at the basal cisterns and Sylvian fissures. c: Noncontrast-enhanced CT scan in a different patient shows the way of the Sylvian fissure slightly denser than the normal brain parenchyma with a calcification (curved arrow). d: Contrast-enhanced CT scan shows thickening and enhancement of the left middle cerebral artery related to arachnoiditis and vasculitis (arrow).

ease predominates in the supratentorial compartment and shows some predilection to be located near the cisterns, fissures, sulci, and ventricles.

In comparison with cysticerci involving skeletal muscle, which calcify almost invariably within 5 years, the cerebral cysts show incomplete and less frequent calcification in from 1 to 5 years. The size of the calcification is about one-quarter of that of the original lesion; calcification occurs in approximately 64.7% of cases. It is the most common finding and results from calcium deposition in dead larvae (Fig. 6).

Other, less common presentations of the parenchymal form are single or multiple homogeneous nodules observed in the contrast-enhanced scan, without the characteristic cystic component and with or without surrounding edema. The most unusual parenchymal lesions show as an isodense, single mass lesion that enhances homogeneously with contrast administration. These uncommon forms may mimic primary brain tumor or metastatic disease.

Brain infarctions are secondary or indirect forms of presentation of meningeal cysticercosis, manifested in the scans in a fashion similar to infarcts of other origin. Brain atrophy may be another secondary manifestation in cases of...
Figure 10. Sequelae of basal arachnoiditis and parenchymal cysticercosis. a and b: Communicating hydrocephalus. Note associated multiple parenchymal calcifications. c: Scan from a different patient showing cortical and subcortical atrophy, parenchymal calcifications, and ex vacuo hydrocephalus.

Figure 11. Intracranial cysticercosis, intraventricular form. a: Noncontrast-enhanced CT scan shows deformity and dilatation of the fourth ventricle. b: Contrast-enhanced CT scan shows annular, peripheral enhancement of the cysticercus cyst. A lesser degree of dilatation is seen in the supratentorial ventricles. A right temporal calcification is evident.
proven cysticercosis; cases of focal atrophy may be explained by previous infarcts, and generalized atrophy could be incidental. There has been no proof of a direct cause and effect relationship.⁹

**Meningeal Form**

The meningeal type of cysticercosis shows up on CT scans as single or multiple cystic lesions firmly or loosely attached to the leptomeninges, usually at the base of the brain (Fig. 7a and b). When they are present over the convexity they can excavate into the cortical gray matter.³ The racemose variety of the parasite shows predominance in the subarachnoid space, where it encounters less pressure and resistance and is thus allowed more expansion. Therefore, the racemose variety may grow as a large cyst, up to 10 cm in diameter. It presents, sometimes, as a conglomerate or as multiloculated cystic lesions, usually found at the base of the brain or Sylvian fissure⁶ (Fig. 8a and b). These lesions also mimic congenital cysts or cystic tumors affecting any cistern or fissure. The mass effect that these lesions produce is variable and, depending on their size, may produce intracranial hypertension, compress vascular structures and ventricles, and even produce herniations. The subarachnoid space is usually distorted, even with small cystic lesions. As in the parenchymal form of the disease, the cysts may also calcify¹⁰ (Fig. 7a and 7b).

When there is compression of vessels by the cystic mass, brain infarction may develop; however, ischemic lesions may also result from vasculitis.⁵,⁸,⁹,²⁸ In cases of subarachnoid vasculitis, the contrast-enhanced CT scan most often is normal, but occasionally asymmetric thickening of some vessels, such as the middle cerebral artery, may be seen.

Cysticercus at the base of the brain offer distinctive features explained on the basis of pathologic findings.³

The contents of degenerated or ruptured vessels are mixed with CSF, which may explain the severe inflammatory reaction in the subarachnoid space that may persist for a long period after the death of the parasite.³ This inflammatory process causes considerable thickening of the leptomeninges, with subsequent adhesions and ventricular dilatation. This may be secondary to blockage of the absorption pathways of CSF, which leads to communicating hydrocephalus⁵,⁶,¹⁰ (Figs. 10a and 10c), or to obliteration of the Sylvian aqueduct by the extrinsic process. Sometimes the distinctive CT features of this arachnoiditis include an isodense configuration of the Sylvian fissure and basal cisterns in the noncontrast-enhanced scan. When contrast medium is administered, a diffuse leptomeningeal enhancement in the previously isodense subarachnoid space can be seen, mimicking extravasation of the contrast agent⁴,¹⁰,¹²,²¹ (Figs. 9a–9d). This appearance does not occur frequently, and, if present, it will persist to a lesser degree in follow-up scans for several months. Most of the time, basal arachnoiditis will be recognized only by the sequelae of the process manifested by hydrocephalus on the CT scan (Fig. 10a and 10b).

**Intraventricular Form**

In most cases, the intraventricular type of involvement is detected only by the presence of hydrocephalus. This is produced by single or multiple cysts large enough to obliterate the Sylvian aqueduct, outlet foramina of Luschka, Magendie, or Monro, or by complete obliteration of the fourth, third, or lateral ventricles.¹⁰,³⁰ The most common presentation is a single parasite lodged in the fourth ventricle ⁵,¹⁰ (Figs. 11a and 11b, and 13b). The cysts may float freely or be attached to a pedicle that allows a ball-valve effect. They can also be firmly attached to the walls of the ventricle or to the choroid plexus.¹,¹²,³⁰ The cysts show the same density in noncontrast- or contrast-enhanced scans and will not be seen most of the time. Their presence may be suspected if there is disproportionate dilatation of the affected area, although occa-
sionally an annular, peripheral enhancement may be seen in large lesions\(^\text{12}\) (Fig. 11b).

Smaller, nonobstructing intraventricular cysts or vesicles may be recognized also by a ring of enhancement, probably related to the inflammatory reaction of the adjacent ependyma or choroid plexus on which these vesicles can be attached and the concomitant capillary proliferation mentioned before\(^\text{12}\) (Fig. 12). In some cases, the parasite is not the primary cause of obstruction but may produce ependymitis that can obstruct the free pathway of CSF at any level within the ventricular system and also produce hydrocephalus.\(^\text{54}\)

In cases of suspected intraventricular cysts, the diagnosis can be confirmed by both CT and conventional metrizamide Ventriculography\(^\text{8,10,12,28,29}\) (Figs. 13a and 13b). This is a relatively noninvasive procedure performed in patients who have ventriculoperitoneal or ventriculoatrial shunts. The procedure is now widely performed because of the low toxicity of this water-soluble contrast medium, which is used routinely in myelograms. The contrast medium

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**Figure 13.** Intraventricular and subarachnoidal cystercerosis on metrizamide ventriculography. a: The cysticercus vesicle shows up as a hypodense filling defect with fluid density within the right lateral ventricle. This lesion is delineated by the metrizamide occupying the rest of the ventricles. b: Another patient with a large cysticercus lodged in the fourth ventricle, which appears dilated (closed arrows). The temporal horns are opacified with metrizamide (open arrows) and are dilated. No contrast is seen in the fourth ventricle because of the large cyst. c: Scan from a different patient. Delayed axial transverse scan shows multiple cystic lesions occupying the proximal right Sylvian fissure and cisterns behind the dorsal sellae (arrows). d: Coronal scan in the same patient (c) showing the dilated cisterns due to the cystic lesions (arrows). [Cases (a) and (b) by courtesy of Daniel Vasconcelos, M.D., National Medical Center, E.M.S.S., Mexico, D.F.]
I"l is injected into the lateral ventricles by a transvalvular percutaneous puncture, by a fine needle, in the antichamber of the shunting system. The administration of 3–5 ml metrizamide at a concentration of 200–250 mg/ml will be enough to allow recognition of the lesions, their location, number, size, shape, relation to adjacent structures, motility, and the exact site of obstruction. The entrance of contrast material to the interior of some cystic lesions has recently been described. The ventricular injection and delayed CT images, or the contrast medium given by a lumbar puncture in patients without hydrocephalus, can be useful procedures in cases of suspected cysts in the subarachnoidal location (Figs. 13c and 13d).

**Mixed Form**

A variety of combinations of forms of presentation may be found in the mixed form of this disease. Parenchymal cysts can be associated with intraventricular or arachnoidal lesions. Intracranial cysticercosis can also be associated with spinal, orbital, muscular, subcutaneous, and even pulmonary involvement (Figs. 14 and 15). Myelography is the procedure of choice in suspected spinal cysticercosis. Ultrasound can demonstrate easily the intraventricular location of the parasite as a small, movable cystic collection or as a small, echogenic image surrounded by the vitreous space (Fig. 14c). On CT examination, the lesion is demonstrated if it is calcified or if there is a ring of enhancement in the contrast-enhanced scan, usually in lesions attached to the inner wall. Otherwise, the vesicle may be isodense with the fluid of the chamber and will not be distinguishable (Fig. 14f).

The findings of intracranial cysticercosis in conventional radiographs are limited. Skull films can demonstrate small, oval or round calcifications, 3–12 mm in size, with an additional

![Figure 14. Intracranial parenchymal cysticercosis associated with extracranial disease in the same patient.](image)
small density situated eccentrically within the calcification that represents the scolex. When the disease is manifested by chronic intracranial hypertension, widening of sutures, erosive changes at the sella turcica or tip of the petrous ridges, and prominence of convolutional markings in the inner table may be present. Air ventriculography and cerebral angiography are less frequently used in the diagnosis of the disease because of their invasive nature and lesser accuracy, compared with CT.

Nuclear medicine brain scans are usually negative, although recently cysticercus antibodies labeled with indium have been used. These show preferential uptake in intracranial lesions. An accuracy close to 100% has been reported for this method. Further investigation of this procedure is needed for conclusive data; however, it may be valuable as a less expensive screening test in the presence of suspicious but nonconclusive CT scans. It may also be useful in determining activity of the disease or response to treatment.

The treatment of intracranial cysticercosis varies according to the location of the disease, symptomatology, and complications. In cases of a single cyst or vesicle with or without focal edema, no treatment is usually required unless...
Figure 16. Parenchymal cysticercosis. Evolution after treatment with Praziquantel. a: Noncontrast-enhanced CT scan showing multiple areas of edema. b: Contrast-enhanced CT scan showing multiple ring lesions. c: Noncontrast-enhanced CT scan 6 months later, after treatment with Praziquantel, shows that the edema has resolved. There are two parenchymal calcifications not seen in the first scan. d: Contrast-enhanced CT scan shows resolution of some cystic lesions. Others have decreased in size.

Figure 17. Parenchymal cysticercosis treated with Praziquantel. a: Multiple cystic lesions in both cerebral hemispheres without edema. Several of the lesions show the scolex in the lumen. b: Two months later, after treatment with Praziquantel, there is considerable improvement. Most of the lesions have disappeared. The residual cystic lesions do not show images of the scolex.
Figure 18. Parenchymal cysticercosis. Early changes after treatment with Praziquantel. a: Pretreatment scan shows two cesticercus vesicles with a thin ring of enhancement. b: One and one-half months later, the right parietal lesion is smaller. The left hemisphere lesion shows some perilesional edema and the ring of enhancement is thicker and better defined. These changes are probably related to the inflammatory reaction observed after the death of the parasite.

the lesion acts as an irritative area causing seizures. Then, anticonvulsant drugs and close follow-up with serial examinations will determine the evolution of the process and the need for further treatment. In the generalized encephalitic stage with multiple vesicles, diffuse edema, and intracranial hypertension, specific medications to treat mainly the hypertension and symptomatic drugs as needed.\(^{10,17,27,36}\)

The medical treatments directed specifically to the parasite include several types of antiparasitic drugs that destroy the cesticercus cyst and larva without secondary damage to adjacent normal tissues and without triggering allergic or anaphylactic reactions. These drugs include fluobendazole\(^{10}\) and metrifonate.\(^{41}\) Although they have been proven to be relatively effective against cesticerci, their use has been limited, despite the favorable results reported especially for the latter. The association of metrifonate and atropine sulfate has decreased considerably the undesirable cholinergic effect of metrifonate.\(^{10}\) More recently, another drug, Praziquantel,\(^{10,17,39,42}\) which is an antihelmintic with activity against all known species of Schistosoma, has been proven efficacious in treating selected patients with parenchymal or subarachnoid, well-defined cesticercus cysts without hydrocephalus.\(^{35}\) Serial CT scans have demonstrated the disappearance of some cysts during and after treatment with this drug (Figs. 16 and 17). Most of the cysts show a decrease in size or some signs of involution, with more thickness of the ring of enhancement or even diffuse enhancement in a smaller lesion. Sometimes, during treatment, a small, perilesional, low-density area in relation to focal edema may be seen, which is probably related to the granulomatous reaction of cerebral tissue occurring at the death of the parasite, with spillage of foreign proteins\(^{4,45}\) (Fig. 18). The overall improvement in the parenchymal nonencephalitic form of the disease with Praziquantel has been up to 95\%.\(^{35}\) Some selected cases of cysticercosis in the encephalitic phase, without clinical intracranial hypertension, have also shown an impressive response, with disappearance of most of the vesicles and edema, and apparent acceleration of the mineralization of some lesions, which can be calcified in less than a 6-month period\(^{40}\) (Figs. 16 and 17). There is no proof of Praziquantel’s effectiveness in cases of intraventricular or intracocular cysticercosis, but, in theory, it might be extremely limited. Praziquantel is also effective against the adult Taenia solium.\(^{41}\)

The surgical treatment of intracranial cysticercosis is limited to the removal or drainage of cysts, mainly the racemose variety that produce significant compression or herniation, or the single, localized and surgically accessible lesion that produces intractable seizures\(^{16}\) (Fig. 19). Perhaps the most common surgical procedures used at present in intracranial cysticercosis are ventriculostomy or peritoneal shunts for cases of arachnoiditis and communicating hydrocephalus, and also in obstructing hydrocephalus caused by either ependymitis or intraventricular cysts.\(^{5,15,26}\) The surgical removal of ventricular cysts may be performed on rapidly enlarging, unattached, and accessible lesions.\(^{8,30}\) CT is useful not only in the diagnosis of cys-
Cysticercosis but also in the evaluation of the natural behavior of the disease in response to medical or surgical treatment.

The problem of human cysticercosis is complex, and, without question, the best form of therapy is preventive medicine. Improvement of personal hygiene, better public sanitation, and careful pork meat inspection are important measures because the prevention of cysticercosis depends ultimately on reducing the incidence of human taeniasis.

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Optokinetic Dissociation, Saccadic Hypomotility, and Sakkidierung

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Case History

A 32-year-old man was seen in ophthalmologic consultation for abnormal ocular motility. At 27 years of age, he had begun to develop progressive cerebellar dysfunction manifested by gait ataxia, dysarthria, and difficulty in handwriting. There was a remarkable family history of cerebellar dysfunction in his mother, who developed progressive cerebellar ataxia and dysarthria at the age of 28, and in his younger brother, who at age 28 was developing a similar clinical course. There was no history of alcoholism, long-term Dilantin use, head trauma, or carcinoma.

On physical examination, the patient was alert and mentation was normal. He had a scanning type dysarthria, marked titubation of the head, facial hypomimia, and intention tremor. Cranial nerves were intact without evidence of nystagmus. On sensory testing there was impaired vibratory, pin-prick, and light touch sensation. Proprioception was intact. Cerebellar testing revealed truncal and appendicular ataxia with significant past pointing found bilaterally. Deep tendon reflexes were 0/4 to 1/4 in all extremities. There was no occulopalatal myoclonus.

Ophthalmologic examination revealed normal acuity, normal visual fields, and intact pupils. Optokinetic responses were abnormal, with horizontal-vertical dissociation manifested as foreshortened horizontal responses and essentially absent vertical responses. Sakkidierung (cogwheel eye movements vertically and horizontally) was present bilaterally.

Blood chemistries, thyroid function tests, and B12 and folate levels were normal. Cerebrospinal fluid (CSF) was microscopically and culture negative but exhibited a slightly elevated protein concentration of 36 mg/dl. Oligoclonal banding was negative.

The radiologic evaluation included computed tomography (CT) and magnetic resonance imaging.

Discussion

The initial CT scan (Fig. 1, left) illustrates a generalized enlargement of the CSF spaces surrounding the cerebellum and the pons. A more cranial section (Fig. 1, right) demonstrates that the sulci of the cerebral hemispheres as well as the lateral ventricles are normal in size and contour. This implies that a local rather than general atrophic process is occurring. Radiologically, the cerebellum and the pons are affected grossly, but it is difficult to determine which, if any, specific nuclei are atrophic. The magnetic resonance image (Fig. 2) is at a higher anatomic level than the CT scan in Fig. 1 (left). The pulse sequence used (spin echo, TR = 1.5 s, TE = 35 ms) is somewhat T1 weighted and thus is useful for anatomic detail. It also demonstrates atrophy of the cerebellum and confirms the results shown by CT. Of importance, however, is that various other T1 and T2 weighted pulse sequences failed to reveal any focal areas of abnormal signal within the atrophic areas. The cerebellum and pons have essentially the same relaxation times as the surrounding normal parenchyma and thus are interpreted as being atrophic neuronal tissue without coexistent inflammation, ischemia, edema, or malignancy.

In patients presenting with the progressive onset of cerebellar dysfunction as the dominant...
feature of the clinical picture, CT, with emphasis on the posterior fossa, has the highest diagnostic yield in the imaging evaluation. A clinical distinction must be made between a degenerative process involving the cerebellum, such as the presence of a mass lesion in the posterior fossa, or a noncerebellar cause for ataxia, such as proprioceptive sensory loss ("sensory ataxia") in labyrinthine pathology.

Often, demyelinating processes will present with signs of abnormal cerebellar function, as will vascular insufficiency syndromes.

In this case, degeneration of the cerebellum and pons was demonstrated but a precise diagnosis can only be suggested from the radiologic findings. In addition, once the finding of cerebellar atrophy is made, historical information, laboratory results, and physical examination must be integrated to arrive at a final diagnosis. This is because a multitude of acquired and inherited disorders exist in which cerebellar atrophy is present to various degrees. Atrophy of other central nervous system structures will aid in etiologic determination, as was the case here when pontine atrophy was found.

Table 1 lists the more common causes of cerebellar atrophy. Radiologic evidence of cerebellar atrophy with thinning of the middle cerebellar peduncles and a small wedge-shaped pons is quite characteristic for olivopontocerebellar atrophy (OPCA).1 A family history of the disorder can be found in about 50% of documented cases,2 and thus was contributory in this patient. There was no history of alcohol abuse, Dilantin use, or carcinoma; thus, the ac-

Figure 1. Noncontrast-enhanced computed tomography in the axial plane (left) shows enlargement of the prepontine cistern (white arrow) and the ambient cisterns (black arrows). The fourth ventricle (curved arrow) is markedly enlarged and the cerebellar sulci (arrowheads) are prominent. The higher section (right) is well above the tentorium and shows normal lateral ventricles and sulci.

Figure 2. Magnetic resonance imaging (pulse sequence is spin echo, TR = 1.5 s, TE = 35 ms, 0.35 T) section in the axial plane shows prominent superior vermal sulci (arrowheads) and enlarged ambient cisterns (arrows).
Figure 3. Noncontrast-enhanced computed tomography in patient on long-term Dilantin use. The fourth ventricle is markedly enlarged and the cerebellar sulci are prominent. Note the prepontine and ambient cisterns are normal as compared with those in Fig. 1 (left).

quired causes of cerebellar atrophy could be excluded. The presence of extrapyramidal signs (sakkidierung) and parkinsonian features (facial hypomimia) are quite variable in patients with OPCA.2,3

In 1891, Menzel4 described a disorder manifested clinically by cerebellar dysfunction and characterized pathologically by atrophy of the cerebellar cortex, inferior olives, gray matter of the pons, and middle cerebellar peduncles. Spinal cord changes were also noted, and an autosomal dominant mode of transmission was apparent. De'jerine and André-Thomas5 in 1900 described a similar disorder that was sporadic in nature. Both of these early descriptions would currently be classified as OPCA.

OPCA is a well-defined entity distinct from cerebellar cortical atrophy (Holmes type), in which pontine nuclei are unaffected, and from Friedreich's ataxia, which predominantly affects the spinal cord. However, OPCA is essentially a term that encompasses a heterogeneous series of diseases whose only common feature is the loss of neurons in the ventral pons, inferior olives, and cerebellar cortex.6

In general, the disease begins in late middle life, with steady progressive ataxia and dysarthria. Gait ataxia was the initial symptom in 67% of the 117 pathologically proven cases studied by Berciano.2 Nystagmus is not a frequent finding and was present in only 10% of cases of familial OPCA and 20% of cases of sporadic OPCA. As the disease progresses, deep tendon reflexes tend to be lost, plantar responses are often extensor, and parkinsonian features develop. Dementia and autonomic dysfunction become apparent to variable degrees. Retinal degeneration and ophthalmoplegias are seen occasionally. Palatal myoclonus is an uncommon associated sign, but when present it is almost pathognomonic for OPCA.

Pathologically, the pons, middle cerebellar peduncles, cerebellar cortex, and olives are atrophic. The corticospinal tracts are preserved but the pontine tegmentum and cerebellar projections atrophy, giving the pons a wedge-shaped appearance. The cerebellar Purkinje cells are virtually lost and there is cell loss in the pontine nuclei and inferior olives. The dentate nuclei are frequently gliotic. The spinal cord shows variable degeneration of the posterior columns and the corticospinal tracts, with the cells of the dorsal nuclei and the intermedio-lateral cell columns being highly atrophic. In addition, gliosis and neuron loss is commonly found in the putamen and the substantia nigra, thus forming a basis for extrapyramidal findings.7

Recently, a reduction of noradrenaline in the cerebellum of patients with familial OPCA has been described.8 This most likely reflects a degeneration of the locus ceruleus noradrenergic system. An in vivo biologic marker for OPCA has yet to be identified, although a reduction in leukocyte glutamate dehydrogenase activity was found in a handful of sporadic cases.8 A biochemical defect may be responsible for pathogenesis, but the basic etiologic mechanism in the development of OPCA remains unknown.

The continuing development of magnetic res-
onance imaging modalities and the use of paramagnetic contrast agents such as gadolinium (Gd-DTPA) may permit visualization of fine anatomic detail allowing the measurement of the cerebellum, the brainstem, and even individual nuclei, rather than having to define atrophy on the basis of enlargement of the surrounding cisterns. This obviously would prove useful in increasing the understanding of the cerebellar syndromes.

References


David G. Cogan, M.D.

David G. Cogan has been elected to the Board of Trustees of the Massachusetts Eye and Ear Infirmary. Cogan is Director of Neuro-ophthalmology at the National Eye Institute, Bethesda, Maryland.

A noted physician, researcher, and author, Cogan was educated at Dartmouth College and Harvard Medical School. He served as Director of the Howe Laboratory of Ophthalmology at the Massachusetts Eye and Ear Infirmary from 1943 to 1973, and as Chief of Ophthalmology at that institution during the 1960s. The Infirmary's David G. Cogan Eye Pathology Laboratory was named in recognition of Cogan's achievements and his contributions to the science of eye pathology.

Founded in 1824, the Massachusetts Eye and Ear Infirmary is a center for the treatment and study of disorders of the eye, ear, nose, and throat; it is a teaching affiliate of Harvard Medical School.