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R. John Leigh

New Editorial Office Address

Effective June 1, 2001, all manuscript submissions, editorial correspondence, and calendar listings and announcements should be sent to:

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Message From the Editor

This issue marks the completion of my tenure as Editor-in-Chief of the Journal of Neuro-Ophthalmology. The North American Neuro-Ophthalmology Society has named Dr. Jonathan Trobe to succeed me. Dr. Trobe will assume the editorship with the September 2001 issue, and I know the journal will flourish under his able direction. As I take my leave, I would like to share a few thoughts on how our field has developed and the journal’s key role in advancing neuro-ophthalmology.

As the field of neuro-ophthalmology grew in the mid-1950s, a serious interest arose in documenting our fascinating case material. The major players included Frank Walsh, A. Kestenbaum, M. Bender, David Cogan, W. F. Hoyt, J. Lawton Smith, and a host of others. By the end of the 1960s, a group of neuro-ophthalmic practitioners formed the Neuro-Ophthalmic Pathology Club, which met on an irregular annual basis. An annual postgraduate course in neuro-ophthalmology was initiated at the University of Miami under the aegis of J. Lawton Smith.

In 1978, many of the leaders in neuro-ophthalmology met in San Francisco to discuss the creation of a journal of neuro-ophthalmology. In spite of a “no” vote by the group, Dr. Smith, with the support of Masson Press, created the Journal of Clinical Neuro-Ophthalmology, serving as editor-in-chief. Published quarterly since its inception, its name changed to the Journal of Neuro-Ophthalmology when the North American Neuro-Ophthalmology Society adopted the journal as its official publication in 1994. Case reports, editorials, and commissioned reviews initially made up a majority of the printed pages. As time passed, the amount and diversity of material available for publication increased in all facets. During the past few years, the Walsh Society and the North American Neuro-Ophthalmology Society amalgamated under the wing of the North American Neuro-Ophthalmology Society, which sponsors the journal. Under these circumstances, the journal will be one of the driving forces in neuro-ophthalmology for the foreseeable future.

As its second Editor-in-Chief, from 1995 to 2001, I would like to express my gratitude for the help I have received from the editorial board and the publishers. I am grateful to those who have submitted papers. I thank Margaret Kealy, Editorial Assistant, who has supplied the necessary logistical help almost single handedly, and Nancy Megley, Publisher, for their continued support through the years.

God speed to my successor, Dr. Jonathan Trobe, and the new editorial board.

Ronald M. Burde, MD
Editor-in-Chief
Systemic Disease and Neuro-Ophthalmology: Annual Update 2000 (Part II)

Larry P. Frohman, MD

In this issue, we will update the general, neurologic, and ocular manifestations of four interrelated rheumatologic disorders: Sjogren syndrome; scleroderma; calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasias (CREST) syndrome; and Raynaud disease/phenomenon. Although these disorders are rarely reported to be associated with neuro-ophthalmic disease, recent expansion of these clinical syndromes and improved understanding of their etiopathogenesis will likely lead to better recognition and their more frequent implication in visual and neurologic disease processes. This update is not meant to be a comprehensive review article on these entities but rather an update on the newer features of interest to the neurologist, ophthalmologist, and neuro-ophthalmologist.

SJOGREN SYNDROME

The original description of Sjogren syndrome (SS) was a triad of dry eyes, dry mouth, and rheumatoid arthritis (1). Like many of the rheumatologic syndromes, SS may be an isolated entity (primary SS), or as secondary SS, it may be a feature of a broader autoimmune/rheumatologic illness, including entities such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosus (SLE, e.g., 20% of patients with SLE develop secondary SS). Sjogren syndrome is not rare; it occurs in 2 to 3% of adults and is more common in women. Five percent of cases have onset of symptoms earlier than 12 years of age (2).

Generally, the neuro-ophthalmologist encounters SS when assessing a patient with unexplained ocular pain, and a diagnosis of dry eye (possibly in conjunction with other related symptoms) is made. SS, however, can have many systemic, neurologic, ocular, or neuro-ophthalmic manifestations beyond a dry eye or mouth.

General signs and symptoms of Sjogren syndrome

The classic symptoms of SS are caused by lymphocytic infiltration of exocrine glands. Oxholm and Asmus sen (3) have proposed a new classification system for clinical involvement in primary SS, dividing the picture into three exocrine and four nonexocrine types (Table 1).

Anaya et al. (4) reported on the spectrum of illness in men, raising the question of whether the course is different in men than women (the disease is much more common in women). They pointed out that in their series of 13 men with primary SS, keratoconjunctivitis sicca (KCS) was the presenting sign in 62%, with extraglandular features being the presenting sign in the rest. Throughout the course of their illness, 92% of these men developed some extraglandular manifestation, with polyarthralgia and lymphopenia being the most common. As for serologic assays, they reported that antinuclear antibodies were abnormal in 85%; rheumatoid factor was elevated in 73%; and anti-SSA, anti-Rho, anti-LA, and anti-SSB were positive in 62% and 46% of cases, respectively. Based on this small series, they conclude that the incidence of extraglandular manifestations and serologic abnormalities is not different in men and women.

The disease can also occur in children. Kobayashi et al. (5) reported four cases of a childhood variant of SS that were accompanied by thyroiditis, interstitial nephritis, or sweat gland inflammation. In one of these four cases, there was also central nervous system (CNS) involvement. The authors point out that this spectrum of illness is not rare in adults with SS.

Ophthalmic involvement and manifestations of Sjogren syndrome

Pflugfelder et al. (6) has studied ways of using ocular tests to identify SS patients from amongst the total pool of dry eye cases. They found that absence of mucosal epithelial membrane mucin expression in the bulbar and tarsal conjunctiva was more typical of SS. Similarity, severe ocular surface rose bengal staining was also a marking of SS.
Neurologic manifestations of Sjogren syndrome

The first reported neurologic manifestations were described by Sjogren (7) himself and were facial nerve paralysis and involvement of the sensory branches of the trigeminal nerve. Lafitte (8) has recently reviewed the neurologic manifestations of SS. He states that they occur in 20% of cases of SS. Nonfocal findings that have been reported include mental status changes and seizures. Multiple cranial neuropathies and sensory and motor polyneuropathies have been seen. In reviewing his personal series of patients with SS, Lafitte finds the incidence of peripheral neuropathy to be 8%, and the KCS complex preceded the neurologic symptoms in nine of ten patients (90%) by a mean of 4.5 years.

In looking at the laboratory evaluation that the patients with neurologic SS have undergone, Lafitte (8) points out that the patients with peripheral neuropathy who have undergone electromyography (EMG) typically demonstrate a pattern consistent with denervation. Nerve conduction velocity (NCV) shows velocities that were normal or slightly reduced, sometimes with prolongation of distal latency. Lumbar puncture is typically normal, and slight pleocytosis or elevation of protein has been seen.

As for pathologic findings, Lafitte (8) reports that peripheral nerve biopsies from patients with SS and peripheral neuropathy have typically shown vasculitis (which may be acute or chronic), or perivasculitis. Demyelination is not uncommon. Muscle biopsies have shown vasculitis, perivasculitis, or myositis. One autopsy case of CNS disease was found and reported necrotizing arteritis of small arteries and arterioles; an autopsy case with spinal cord involvement also showed a necrotizing vasculitis.

Amoura et al. (9) pointed out that although peripheral nervous system manifestations are more common, CNS findings do occur. These manifestations include encephalitis, focal or diffuse involvement of the spinal cord, and acute aseptic meningitis. He states that psychiatric changes are not uncommon in these patients. Sagawa et al. (10) state that the most common psychiatric findings are depression and anxiety.

Belin et al. (11) found that 100% of his series of 14 female patients with SS had abnormalities on formal neuropsychologic testing. The abnormalities were typically frontal lobe syndrome and memory deficits. These findings did not seem to be correlated with other neurologic abnormalities findings on magnetic resonance imaging (MRI) scans but did correlate with the results of 99m-technetium-hexamethylpropylene amine oxide (HMPAO) single photon emission computed tomograph of the brain (SPECT) (see "Diagnostic techniques for Sjogren syndrome").

Govoni et al. (12) systematically studied 87 unselected patients with primary SS (4 men, 83 women) for evidence of neurologic involvement. They found that seven patients had CNS disease (8%), largely a nonfocal illness. Twelve patients (14%) had peripheral nervous system (PNS) disease, largely sensory or sensory-motor polyneuropathy; one patient had CNS and PNS disease. They found that CNS disease tended to occur in the younger patients, and neither serologic assessment nor other extraglandular disease activity served as useful markers for the development of neurologic involvement.

Niemela and Hakala (13) recently reported a case and reviewed the literature on neurologic involvement in SS. Their patient had primary SS and had lymphadenopathy and myositis, after which she developed severe CNS disease, vasculitic lesions on her hands, and a neurogenic bladder attributed to spinal cord involvement. Although she did not respond to corticosteroids alone, she did respond to the addition of cyclophosphamide. Niemela pointed out that the incidence of CNS disease in SS is not well characterized in the literature, with statements ranging from its being rare to being present in approximately 25% of cases. This group feels that MRI is the most sensitive test and cerebral angiography the most specific test for detecting neuro-SS. They also point out that no controlled therapeutic trials have been performed, and the typical therapy of neuro-SS is that of vasculitis.

Escudero et al. (14) reviewed the neurologic involvement in 48 patients (7 men, 41 women; mean age: 58.2 years) with primary SS. The most common CNS features were migraine (52%), neuropsychiatric disease (29%), and focal neurologic deficits (23%). MRI scanning detected small hyperintense subcortical lesions in 51.3% of patients (36.6% in age- and sex-matched controls, P < 0.001). They point out that the coexistence of late onset migraine-like episodes with prolonged sensorimotor deficits and coexisting neuropsychiatric disease may be a typical symptom complex in SS patients who present with neurologic manifestations. In their series, a multiple sclerosis-like course was rare.

Perhaps the highest incidence of neurologic disease was reported by Tajima et al. (15) in a series of 21 female Japanese patients with primary SS. Sixteen of these 21 patients (76%) showed neurologic symptoms. The most common finding was trigeminal neuropathy, seen in

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**TABLE 1.**

<table>
<thead>
<tr>
<th>A) Exocrine types</th>
<th>B) Nonexocrine manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Type 1—surface exocrine disease</td>
<td>1) Type 4—inflammatory vascular disease</td>
</tr>
<tr>
<td>a) Keratoconjunctivitis sicca</td>
<td>a) Vasculitis and perivasculitis</td>
</tr>
<tr>
<td>b) Xerostomia</td>
<td>2) Type 5—noninflammatory vascular disease</td>
</tr>
<tr>
<td>1) Upper airway disease</td>
<td>a) Raynaud</td>
</tr>
<tr>
<td>2) Rhinitis sicca</td>
<td>3) Type 6—mediator-induced disease</td>
</tr>
<tr>
<td>3) Xerophthalmia</td>
<td>a) Hematologic cytopenia, fever, and fatigue</td>
</tr>
<tr>
<td>c) Xeroderma</td>
<td>4) Type 7—autoimmune endocrine disease</td>
</tr>
<tr>
<td>2) Type 2—internal organ exocrine disease</td>
<td>a) Involvement of the excretory parenchyma of the lungs, hepatobiliary system, pancreas, intestinal tract, and kidneys</td>
</tr>
<tr>
<td>a) Involvement of the excretory parenchyma of the lungs, hepatobiliary system, pancreas, intestinal tract, and kidneys</td>
<td></td>
</tr>
<tr>
<td>3) Type 3—monoclonal B-lymphocyte disease (lymphoma)</td>
<td>a) Raynaud</td>
</tr>
</tbody>
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**ANNUAL UPDATE OF SYSTEMIC DISEASE: PART II**

50%. Multiple mononeuropathy was seen in 31% of cases. CNS involvement was only observed in three cases (14%).

van Dijk et al. (16) have looked from the reverse perspective (i.e., has tried to assess the incidence of occult SS in 65 patients with idiopathic axonal polyneuropathy), using an interview focusing on oculomotor and oral sicca symptoms, a physical examination, tests for objective assessment of KCS, serologic investigation, and subbial salivary gland biopsy (done in only 49 of the cases). Three of the 49 (6%) had a biopsy consistent with SS. Although such symptoms were revealed in the study, none of these three patients had spontaneously complained about sicca symptoms. The authors conclude that in patients with chronic idiopathic axonal polyneuropathy, a systematic investigation for Sjogren syndrome should be completed. Parkinson disease has been reported in association with SS. Walker et al. (17) described three cases and cites five more in the literature.

Tumiala et al. (18) have examined the incidence of hearing loss in SS. In comparing 30 patients with SS with 40 age-matched controls, they found that 46% of patients with SS had sensorineural hearing loss compared with 3% of controls. Of note was that of the patients with hearing loss, 64% had positive titers for antikeratin antibodies.

As is the case with many autoimmune diseases, patients with SS may display a clinical syndrome and MRI findings similar to multiple sclerosis. Watanabe et al. (19) described a 40-year-old woman with primary SS who had a slowly progressive neurologic course. Neurologic signs and symptoms included spasticity and monoparesis of the left leg, slurred speech, nystagmus, hyperreflexia, and positive bilateral Hoffmann reflexes and Babinski signs. MRI scanning showed multiple nonenhancing plaquelike lesions in the white matter of the cerebrum and brainstem. Notable serologies included an abnormal antikeratin antibody (spastickeled) and antikeratin/ro antibody. Spinal fluid showed 8 cells/mm³, a protein of 42 mg/dL, four oligoclonal bands, and an elevated IgG index. Because of her dry eyes, lacrimal and salivary secretion tests were performed and demonstrated hyposecretion of tears and saliva. This finding led to a biopsy of the lip with demonstration of destruction of the minor salivary gland ducts with periductal lymphocytic infiltration, which confirmed the diagnosis of primary SS.

**Neuro-ophtalmic manifestations of Sjogren syndrome**

Optic neuropathy is occasionally seen as a manifestation of primary SS, with approximately ten cases having been reported, most recently by Rosier et al. (20) and Harada et al. (21). Rapoport et al. (22) has described the case of a 68-year-old woman with well-documented primary SS (keratoconjunctivitis sicca with abnormalities in salivary gland biopsy and serologic abnormalities) who developed ischemic choroidopathy (shown on fluorescein angiography) and optic neuropathy. The optic neuropathy was accompanied by pain, the disc was swollen, and the visual loss partially responded to prednisone. Several months later, she experienced visual loss in the other eye, associated with hypoesthesia of the left side of the body. Fluorescein angiography indicated that this visual loss was caused by choroidal infarction. Because of symptoms of KCS, a minor salivary gland biopsy was performed, which confirmed the diagnosis of SS. This patient later developed transverse myelopathy.

DeGuzman et al. (2) have described a fascinating case of a 14-year-old boy who presented with a fever and a generalized tonic–clonic seizure. Approximately 1 year later, involuntary spasms of the gastrocnemius and quadriceps muscles and episodes of limb ataxia began; another tonic–clonic seizure occurred. At this point, a poorly documented episode of loss of vision OD that lasted 2 weeks was noted. Six months later, bowel and bladder incontinence and lower extremity numbness were seen. Five months later, he developed what was described as nonerythematous, nontender, right periorbital swelling and reported decreased vision and seeing gray spots.

The ophthalmic exam showed acuities of no light perception OD and 20/20 OS. The right eye showed keratoepitactates and inflammatory cells in the anterior chamber and vitreous. Blood was reported as being present in the neuroepithelium from the optic disc to the ora serrata, with venous tortuosity and intraretinal blood in all four quadrants. An inflammatory nodule was seen anterior to the optic disc. Perivenous sheathing was recorded, especially around the larger veins in the posterior pole. Fluorescein angiography showed significant slowing of venous return and poor arteriole perfusion of the fovea, with diffuse leakage from both veins and arteries, especially on the venous side.

The MRI scan showed a linear focus of abnormal signal in the frontal periventricular white matter on T2 sequences. On T1 sequences, there was enhancement at the level of the right trigeminal nucleus. The spinal tap was remarkable for a mild pleocytosis; no oligoclonal bands were seen, and myelin basic protein was normal. Key serologic findings included an erythrocyte sedimentation rate (ESR) of 52 mm/h, a marked elevation of serum IgG, and a slightly elevated CH50. Antinuclear antibody, anti-double-stranded DNA, anti-ribonuclear protein, anti-SM, anti-SSA (Ro), anti-SSB (La), antiphospholipid antibodies, and antineutrophilic cytoplasmic antibody (ANCA) were all normal. Rheumatoid factor and angiotensin-converting enzyme (ACE) results were not mentioned. The serum anti-Ro converted to positive, and 6 months later, a minor salivary gland biopsy was performed, revealing a pathology of focal lymphocytic stromadenitis, which is consistent with (although not absolutely specific for) SS. The patient was treated with corticosteroids and monthly intravenous cyclophosphamide. On this regimen, his CNS and ocular disease progressed, with bilateral panuveitis, sensorineural hearing loss, and a central facial paresis. He also developed a mild thoracolumbar myelopathy. The CNS disease responded to intravenous corticosteroids, and his mainte-
nance therapy was changed to prednisone and chlorambucil, which controlled his symptoms (2).

Bachmeyer et al. (23) has reported a case of bilateral Adie tonic pupil in primary SS. This patient had antibodies to Ro (anti-SSA). Whereas the patient's necrotizing gingivitis responded to systemic therapy (corticosteroids and antimalarials), the pupillary abnormality did not. The authors postulate that the source of the Adie pupil was an inflammation of the ciliary ganglion.

Diagnostic techniques for Sjogren syndrome

The use of MRI scans in the detection of neurologic lesions in primary SS has recently been studied by Coates et al. (24). The frequency of deep white matter and subcortical lesions was significantly increased in the SS patients (with and without neurologic illness) compared with age-matched controls. The presence of these lesions did not correlate with serologic markers such as anticardiolipin antibody, serum IgG levels, or titers of rheumatoid factor, nor did they correlate well with neurologic signs and symptoms. In addition, corpus callosal lesions were not seen in the SS patients, thereby being a marker that may be used to help differentiate these patients from those with MS.

Kao et al. (25) used 99m-technetium-HMPAO brain images with fanbeam SPECT to study 48 SS patients, all of whom had undergone a normal MRI or computed tomograph (CT) of the brain. In the group with neuropsychiatric symptoms and signs, 53% showed local hypoperfusion in the cortex, whereas only 20% of the group without neuropsychiatric signs had this abnormality. Similarly, hypoperfusion was seen in the basal ganglia and thalamus of 14% of those with symptoms and none without neuropsychiatric symptoms. In those with neuropsychiatric symptoms, the parietal lobes were the most common areas of brain involvement. The authors feel that this method of SPECT scanning may prove to be a sensitive tool for detecting regional cerebral anomalies in SS patients.

Kao also compared the usefulness of 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomograph (PET) scanning and 99m-technetium-HMPAO SPECT scan in patients with neuropsychiatric manifestations of primary SS. It was found that 99m-technetium-HMPAO SPECT was superior, with abnormalities detected in 81% of patients and with the parietal and temporal lobes the most common sites of brain involvement. The authors feel that this method of SPECT scanning may prove to be a sensitive tool for detecting regional cerebral anomalies in SS patients. They state that although the mechanism of this alteration in cerebral blood flow alterations is unknown, it might be the result of diffuse cerebral vasculitis.

SCLERODERMA

Scleroderma is also known as systemic sclerosis or progressive systemic sclerosis. It targets numerous organ systems, including the skin, blood vessels, synovium, gastrointestinal tract, kidneys, heart, and lungs. The subtype known as CREST syndrome will be discussed later.

The lesions of scleroderma are typified by inflammation and fibrosis; the etiology of these lesions is not well understood. One theory is that activated inflammatory cells liberate cytokines, which in turn stimulate collagen production. As in Wegener granulomatosis, the disease may be diffuse or localized. Eighty percent of patients are women (28).

The skin changes are typified by overabundant deposition of collagen, presumably leading to skin thickening, tightness, and diminution of mobility with contracture. Telangiectasia and calcinosis are often seen. A second feature of this disorder is vascular insufficiency and vasospasm. Raynaud phenomenon is a typical feature of scleroderma, occurring in perhaps 95% of cases.

Ophthalmic manifestations of scleroderma

The most recognized feature is KCS, present in as many as 70% of cases. This symptom is complicated by the shortening of the conjunctival fornices (28). Choroidal disease is not uncommon in scleroderma; one series reported that 53% of cases had patchy areas of nonperfusion on fluorescein angiography. The authors point out that this nonperfusion is not detectable on funduscopy (29).

Neurologic manifestations of scleroderma

The CNS is typically spared in scleroderma. A few cases of stroke have been reported, presumably related to fibrosis occurring in artery walls (30). PNS disease is unusual in scleroderma and is typically related to nerve entrapment. When the PNS is involved, a distal mononeuropathy of the median nerve is a typical feature (31). Mouton et al. (32) have recently reported brachial plexopathy in a case of scleroderma. Pulse cyclophosphamide therapy led to improvement of the cutaneous and neurologic manifestations in this patient.

One series reported a much higher incidence of neurologic disease in scleroderma. This group found that 31% of patients (35%) had neurologic findings, consisting of trigeminal neuropathy or polyneuropathy. They also felt that the subpopulation of scleroderma patients harboring the antibodies anti-U1RNP and possibly those with anti-Scl-70 might be more prone to develop neurologic illness (33).

This same group also studied the potential genetic basis for altered immune function playing a role in scleroderma. They reported that patients with neurologic illness had a higher frequency of human leukocyte antigen
(HLA) types DR5 and B8 than scleroderma patients without neurologic illness. They conclude that genetic substrate may be associated with different clinical subsets of systemic sclerosis (34).

Autonomic nervous system dysfunction is not unusual and appears to be a key factor in the development of microvascular, cardiac, and gastrointestinal symptoms (31,35).

Recent evidence has emerged that nerves may be a target in this disorder, independent of direct compression. Malandrini et al. (36) recently performed rectal biopsies on three patients with limited and early scleroderma of the gastrointestinal system. Axonal degeneration with mast cells in close proximity to nerve fibers was seen.

Etiology of scleroderma

It is generally accepted that the fibrosis that is the main feature of scleroderma is secondary to persistent overproduction of collagen. The question is why. Jimenez and Safta (37) pointed out that the overproduction results from altered regulation of expression of the alpha 1(1) collagen gene (COL1A1) in patients with sclerosis.

Recent work by Shi-Wen et al. (38), using fibroblasts from the skin of patients with scleroderma, supports that an upregulation in a gene may cause the fibrosis that characterizes this disorder. They found that the gene that codes for human connective tissue growth factor (CTGF) is consistently present and that the protein that it codes for is seen in cultured fibroblasts of scleroderma patients but not in healthy patients.

Another question that has been raised is whether altered arteriolar response to vasoconstrictors might play a role in the pathogenesis of scleroderma. Flavahan et al. (39) has recently demonstrated that dermal arterioles from skin biopsies of scleroderma patients have increased vasoconstriction in response to alpha-2 adrenergic receptor agonists. They postulate that this finding may play a role in the vasospasm that is a prominent feature of this illness.

As for the basic trigger of the altered gene regulation or vascular sensitivity, Kahaleh and LeRoy (40) point out a line of evidence for unsuspected cytomegalovirus infection being the trigger. This evidence includes the detection of increased levels of anticytomegalovirus antibodies in patients with scleroderma and similarity between the vascular disease of cytomegalovirus and scleroderma.

Diagnostic techniques for making the diagnosis of scleroderma

Salojin et al. (41) has postulated that antiendothelial cell antibody (AECA) may be a marker that allows one to prognosticate disease severity, because it tends not to be positive in those patients with milder forms of scleroderma.

Stucker et al. (42) have used digital subtraction angiography of the digits to study vasoocclusive disease in scleroderma. They studied a total of 29 scleroderma cases, 14 with acroscleroderma and 15 with proximal ascending sclerosis. They found that 27 of 29 (93%) patients demonstrated stenosis. The involvement tended to be more prevalent in the distal upper extremity. The severity of Raynaud phenomenon seen in these patients did not correlate with the angiographic findings.

Heron et al. (43) looked at the usefulness of CT scans of the brain in the detection of intracerebral calcifications in scleroderma. They studied 37 consecutive scleroderma patients with noncontrast brain CT. Of these, 43% had diffuse scleroderma and 57% had the limited form. They found intracerebral calcifications in 32% of their scleroderma patients. Although the age of the patient did not seem to be correlated with the presence of calcifications, the duration of Raynaud phenomenon did, with the duration being twice as long in those with calcifications. In general, the calcifications did not correlate with symptoms—the sole exception being disease of the digestive tract. Calcifications were also seen in the basal ganglia in 30% of patients (the incidence in the population is said to be 0.2–2%). The authors postulate that the calcification is a marker for chronic vascular injury in the disease.

Therapeutic strategies for scleroderma

Trials of the use of immunomodulatory drugs in this disorder have lagged behind that of other entities such as vasculitis. Morton and Powell have recently used cyclosporine and tacrolimus in patients with scleroderma. In a retrospective review of their experience, they found that half of their patients treated with cyclosporine for skin tightness noted improvement. Of the patients treated for digital vasculitis, 25% noted resolution. They also report that most patients could not tolerate the drug. They have a smaller experience with tacrolimus; it appears to be better tolerated than cyclosporine and seems to yield similar results (44).

Numerous agents are being tested for therapy of specific features of this disorder, including the agent sargrelate hydrochloride, which has shown some promise in a small study (45).

CREST SYNDROME

The CREST (Calcinosis, Raynaud phenomenon, Esophageal motility disorders, Sclerodactyly, Telangiectasias) syndrome is considered by most professionals to be a subtype of scleroderma. The first case was reported by Thibierge and Weissenbach in 1910, although the use of what was then ACRST syndrome did not appear until 1964. Identifying the CREST subtype is important; the prognosis is better in this form than in diffuse scleroderma. Fifty percent of CREST syndrome patients demonstrate antcentromere antibodies (as opposed to the diffuse scleroderma type, which is associated with anti-Scl-70 [topoisomerase I] antibodies in approximately 25% of patients or with anti–RNA polymerase III in approximately 20% of patients) (46).

Ophthalmic manifestations of CREST syndrome

Al-Husainy and Deane (47) have reported on a patient with bilateral keratomalacia in CREST syndrome. This woman had CREST syndrome for 18 years and had been using lubricant eyedrops for 7 years for a mild dry eye.
that became symptomatic after cataract surgery 7 years before presentation. She developed paracentral corneal ulceration, which was unresponsive to treatment. The ulcer eventually healed, but she died 10 weeks later. The authors postulate that the ulcer was secondary to xerophthalmia from nutritional deficiency in CREST syndrome.

Santos et al. (48) have reported on a patient with CREST syndrome, primary biliary cirrhosis, and bilateral granulomatous uveitis. Proctor et al. (49) have described a case of parafoveal telangiectasia, also known when acquired as idiopathic juxtafoveal retinal telangiectasia, in a patient with CREST syndrome. She presented with visual loss in one eye 11 years after her CREST syndrome manifested. Although the symptoms were monocular, she was noted to have telangiectasia bilaterally in the temporal parafoveal zone, with retinal thickening. The fluorescein angiogram showed enlargement of the foveal avascular zone and leakage from the telangiectatic vessels. The authors suggest that there may be a common pathophysiologic mechanism for the CREST and the retinal findings.

Neurologic manifestations of CREST syndrome

Dyck et al. (50), using the patient population of the Mayo Clinic, identified 536 people with CREST syndrome. Of these, seven (1.5%) had peripheral neuropathy not attributable to another cause. The range of time from the onset of CREST syndrome to development of peripheral neuropathy was from 0 to 25 years. This typically was a multiple mononeuropathy. Sural nerve biopsy was performed in four cases, revealing multifocal fiber loss and perivascular inflammation. Three of the cases either were frankly diagnostic of or suggested necrotizing vasculitis. Note that this finding is similar to what Lafitte (8) has reported as the pathology of peripheral neuropathy in Sjögren syndrome.

Blanco et al. (51) reported two cases of CREST syndrome with extensive cerebral calcification noted on CT scan. The first patient presented with typical systemic symptoms, depression, and mental slowing. During the next 6 months, his cognitive changes progressed; the rest of the examination was normal. His CT scan showed bilateral calcifications in the dentate nucleus, basal ganglia, and subcortical white matter. The second patient developed transient ischemic attacks (express aphasia and right hemiparesis) 1 year after diagnosis of CREST syndrome. Her neurologic exam was normal; her CT scan showed bilateral calcifications of the basal ganglia and faint calcifications of the dentate nuclei and rubral nucleus, with moderate cerebral and cerebellar atrophy. Carotid ultrasonography and Holter monitor were normal; an echocardiogram showed calcification of the mitral valve leaflets with thickening and an ejection fraction of 60%. Aspirin was given, and no further ischemic attacks occurred. The authors postulate, as did Heron et al. (43) in their cases of scleroderma, that chronic vasculopathy led to the calcification.

Heron et al. (52) described two patients with neurologic involvement in CREST syndrome who underwent autopsy. One had dementia, and the other had transient ischemic attacks and a balance disorder. Both cases showed extensive wall calcification of small arteries and arterioles in the brain, especially in the basal ganglia and in the frontal lobes and the cerebellar area in the second case. Because no other known cause of the calcification was found, the authors postulated that calcification might be a marker for CREST-induced vasculopathy. Note that this group later performed the study of CT scans in patients with scleroderma, mentioned in the preceding section, "Diagnostic techniques for making the diagnosis of scleroderma" (43).

Kambara et al. (53) have reported a case of myasthenia gravis in a patient with CREST syndrome. Ortiz et al. (54) have reported on a patient with CREST syndrome who developed multiple intracranial aneurysms.

Neuro-ophthalmic manifestations of CREST syndrome

Neuro-ophthalmic disease has not been a feature of CREST syndrome. In the previously mentioned case of Ortiz et al. (54), the patient had bilateral optic neuropathy. The authors postulate that there may have been components of direct aneurysmal compression of the optic nerves and an intrinsic vasculopathy.

Diagnostic techniques for CREST syndrome

This syndrome may overlap with several other autoimmune diseases. Furthermore, other conditions such as rheumatoid arthritis or SLE may evolve into CREST syndrome. Of note is that when this event occurs, it may be heralded by the patients seroconverting to positive for autoantibodies such as the anticientromere antibody (55). Lundberg et al. (56) also reported on the usefulness of an IgG autoantibody against fibrillin as a marker for CREST syndrome in a small group of patients. Although this marker is present for long periods, it is not specific for CREST and is seen in other disorders, such as mixed connective tissue disease.

RAYNAUD DISEASE AND RAYNAUD PHENOMENON

Raynaud disease (RD) is typically a bilateral symmetric illness seen predominantly in women. Raynaud phenomenon may be a prominent feature in RD. Raynaud phenomenon is the typical blanching of the distal digits, often accompanied by pain. A typical color progression of white to red to blue is seen as cyanosis develops from vasospasm. Raynaud phenomenon may be secondary to RD or to other illnesses—especially collagen vascular diseases such as rheumatoid arthritis, scleroderma, or CREST syndrome—or even mechanical causes, such as use of a pneumatic drill.

Raynaud phenomenon is not uncommon. Brand et al. (57), reviewing data from the Framingham study, found
a slight preponderance in women (9.6% of women, 8.1% of men). Eighty-one percent of this was primary Raynaud disease. They found that the most common causes of secondary Raynaud phenomenon were carpal tunnel syndrome, rheumatoid arthritis, and use of beta-blockers.

**General signs, symptoms, and associations of Raynaud disease**

Raynaud phenomenon may be a feature of another disease of interest to neuro-ophtalmologists. Recently a case of Raynaud phenomenon was reported secondary to giant cell arteritis. This biopsy-proven case had angiography, which demonstrated occlusion of the subclavian and axillary arteries with abundant collaterals. Therapy with oral corticosteroids led to resolution of the Raynaud phenomenon, which was attributed to the involvement of the subclavian artery (58).

Another case where Raynaud was a presenting feature of a more widespread systemic disorder was published by Boortz-Marx et al. (59). The patient in this study presented at age 29 with livedo reticularis, hypertension, and Raynaud phenomenon. Antiphospholipid antibodies were absent. This patient underwent leptomeningeal biopsy, which revealed a granulomatous infiltration. Ultimately, a final diagnosis of Sneddon syndrome was established.

It has long been known that Raynaud phenomenon may be related to repetitive vibrational injury, such as occupational use of a pneumatic drill. Cherniack et al. (60) have shown that these abnormal vascular responses were worse in smokers. Furthermore, among those people who ceased their occupational exposures, those who also stopped smoking had much fewer symptoms of Raynaud phenomenon than those who continued smoking.

Raynaud phenomenon may also be iatrogenic. It appears to be a consequence of therapy with both interferon-alpha and -beta. Ene et al. (61) reported on a patient who had preexisting Raynaud in chronic hepatitis C. This patient was treated with interferon-alpha-2b and developed episodes of severe headache, worsening of the Raynaud, and blurred vision that occurred within 1 hour of the interferon injection and resolved within 1 day. Cruz’s patient did not have preexisting Raynaud and developed severe manifestations 2 weeks after beginning interferon-beta therapy for multiple sclerosis, including digital necrosis and livedo reticularis. These manifestations improved after discontinuation of the therapy (62). Raynaud (with livedo reticularis) has also been described as a result of methimazole therapy for Grave disease (63).

**Ophthalmic manifestations of Raynaud disease**

Terwindt et al. (64) has described a Dutch family with a pedigree that features Raynaud phenomenon in conjunction with migraine and a vascular retinopathy. Although the age of diagnosis of the retinopathy ranged from 26 to 62 years, the authors point out that these patients typically did not consult their ophthalmologist until retinopathy was advanced, so the age of onset is not clear. The younger patients typically had capillary occlusions, whereas the older patients also had large vessels involved. A typical feature was parafoveal telangiectasia and microaneurysm. When the disease affected larger vessels, it tended to involve the arteries more than the veins. Neovascularization and shunt vessels were seen, and 30% of those with retinopathy developed optic atrophy. The authors comment that there seemed to be a disparity between fundus appearance and visual acuity, with the acuity sometimes remarkably spared.

**Neurologic manifestations of Raynaud disease**

Ferraccioli et al. (65) have recently investigated regional cerebral blood flow in patients with Raynaud phenomenon by employing SPECT scanning. The scans were done and then repeated within a week, with tracer injected within 1 minute of completion of a cold test (whereby the patient’s hand is immersed in 4°C water for 15 minutes or until the pain became intolerable).

Among the 12 patients with Raynaud secondary to SLE, 75% had cerebral perfusion defects, as opposed to 57% in SLE cases without Raynaud. Of note was that the cold test elicited new perfusion defects in two cases, and seven of nine (78%) of those who had shown perfusion defects at normal temperatures had worsening in response to cold. No patient without Raynaud showed such a response to cold. Also of note was that there was a significant association between such a response to cold and the presence of antiphospholipid antibody and/or lupus anticoagulant. The authors feel that these findings may be related to the common occurrence of headaches in patients with Raynaud phenomenon, although no patient developed a headache during the cold test.

**Neuro-ophtalmic manifestations of Raynaud disease**

A case of light-induced visual loss has been described in a patient with migraine and Raynaud phenomenon by Safran and Boschi (66). It was felt that this patient, who did not have carotid artery disease, had vasospasm in response to light exposures lasting 5 to 10 minutes. Kuhl et al. (67) have reported a case of trochlear nerve palsy in a patient with recurrent Raynaud of the tongue.

**Etiology of Raynaud disease**

Harel et al. (68) postulate that some cases of Raynaud phenomenon may be an occult manifestation of infection with parvovirus B19. This virus is already known to be associated with erythema infectiosum, transient aplastic crisis, and hydrops fetalis, and it has various rheumatologic symptoms. Harel et al. describe two patients who had onset of Raynaud with generalized polyarthralgia, and the entire work-up was negative except for the parvovirus titers. They postulate that immune-mediated endothelial damage leads to platelet activation and vasoconstriction and recommend that in cases of Raynaud of unknown etiology, serology for parvovirus B19 should be included in the evaluation of the patient. Gashbarri et al. (69) postulate that Raynaud may be another symptom that is attributable to *Helicobacter pylori* infection and claim that eradication of the bacteria leads to improvement in Raynaud.
Therapeutic strategies for Raynaud disease

The traditional therapy for Raynaud has been the use of calcium channel blockers, especially nifedipine. Approximately 67% of patients respond to calcium channel blockers; newer such agents with fewer side effects (amlodipine, isradipine, nicardipine, and felodipine) also appear promising (70).

Other classes of agents are being tested for Raynaud. Dziadzio et al. (71) have studied losartan, an antagonist of angiotensin II-receptor type 1, for the management of primary and secondary Raynaud phenomenon. Outcomes such as the severity and frequency of episodes of Raynaud phenomenon and findings on thermography and laser Doppler flowmetry were used. In this series, the drug was tolerated and had significant beneficial effect. Other agents that have shown promise for Raynaud in scleroderma include prazosin and iloprost (72–74), although another group did not find the latter agent, a prostacyclin analog, to be effective (75). Varcha-Agular et al. (76) report that misoprostol, a prostaglandin E1 analog, is approximately as effective as nifedipine.

A novel approach to therapy of the vasospastic component of Raynaud phenomenon is being investigated by Tucker et al. (77). This group, using the theory that some of the vasospasm is related to impaired generation of or lack of sensitivity to nitric oxide, has developed a gel that locally generates nitric oxide. They found that this gel can increase local circulation in Raynaud patients and healthy people.

Raynaud is 60% more prevalent in patients with carpal tunnel syndrome than in the general population. Chung et al. (78) report that there are selected cases where surgical decompression of carpal tunnel syndrome may alleviate Raynaud phenomenon in patients with both syndromes. The authors caution that to use this approach, professionals must carefully select patients who do not have Raynaud as part of an underlying systemic illness.

Much exciting work is being done in the diagnosis, therapy, and understanding of the pathogenesis of these related disorders. It is hoped that increased awareness of the potential for neurologic and ocular findings will lead to increased recognition of the underlying conditions, allowing for specific therapies to be used.

REFERENCES


Oculopalatal Tremor With Tardive Ataxia

Eric Eggenberger, DO. Wayne Cornblath, MD. and Donald H. Stewart, MD

Oculopalatal tremor consists of palatal tremor and pendular nystagmus and may develop in a delayed fashion after an acute brainstem lesion. Delayed sequelae are generally restricted to the eyes and branchial-derived muscles, such as those of the palate. We report three cases of oculopalatal tremor that subsequently developed disabling delayed-onset ataxia and emphasize the potential for this significant complication after larger bilateral acute brainstem lesions with sparing of the inferior olive.

Key Words: Oculopalatal tremor—Ataxia—Nystagmus.

Oculopalatal myoclonus, perhaps more accurately described as oculopalatal tremor (OPT), consists of pendular nystagmus with palatal tremor. OPT typically presents in delayed fashion weeks to months after an acute brainstem lesion. Most reports describe continuous palatal tremor in association with vertical pendular nystagmus; however, variations have been noted to include monocular, horizontal or torsional nystagmus, and involvement of other branchial-derived muscles (1). Although patients with OPT often exhibit symptoms related to the acute lesion, the delayed sequelae are typically restricted exclusively to the eyes and palate. Cases of OPT at two institutions were reviewed for the presence of delayed-onset ataxia. We report three cases of OPT with associated delayed occurrence of progressive cerebellar system dysfunction producing disabling ataxia.

CASE REPORTS

Case 1

A 70-year-old man with hypertension experienced the sudden onset of dysarthria, mild left hemiparesis, dysphagia, and horizontal diplopia in February 1992. A computerized tomography (CT) scan of the brain revealed a 3 x 1-cm pontine hemorrhage. After rehabilitation, he improved neurologically with resolution of the diplopia within 3 months. By July 1992, he no longer required a cane, and by September 1992, he was able to ambulate independently and perform strenuous chores, such as carrying firewood on uneven ground and assisting (without any supportive devise) in the building of his daughter’s barn. However, in early 1993, he experienced the insidious onset of primarily gait ataxia, which slowly progressed during 12 months by fall 1993. He required assistance with at least a single-point cane to maintain standing balance and ambulation, and he stopped driving in late 1993 because of new visual symptoms. These symptoms included the inability to read signs when traveling in a car; inability to read scrolling print, such as stock reports on television; and difficulty with visual tracking, such as reading a newspaper. On rare occasion, he noted oscillopsia, only with the OD closed. He was unable to ambulate without his wife’s assistance by December 1993, and he began using a wheelchair when a walker became insufficient to maintain balance. Magnetic resonance imaging (MRI) in 1994 revealed bilateral high signal within the inferior olive on T2-weighted images and a 3 x 0.7-cm linear pontine abnormality consistent with residual blood products (primarily hemosiderin) (Fig. 1 and Fig. 2). Initial neuro-ophthalmologic examination in January 1995 revealed normal afferent visual function. The motility examination documented asymmetric pendular, torsional nystagmus with a slight vertical component, greater in the OS. This nystagmus occurred in synchrony with palatal and respiratory muscle movements (as evidenced by a respiratory pattern punctuated by the superimposition of small amplitude rhythmic inspirations) with an estimated frequency of 2 to 3 Hz. Impaired suppression of the vestibular ocular reflex was observed in the horizontal plane bilaterally via rotary chair testing (patient gain at 50 degrees/s, 0.160 Hz was 0.43; normal < 0.14). A left hypertropia of 1 to 2 prism diopters was present in primary position and left gaze. Marked and disabling appendicular, axial, and gait ataxia was severe enough to confine the patient to a wheelchair. Ambulation required the full assistance of at least one person. Palatal tremor, as evidenced by external neck inspection, persisted in sleep, according to the patient’s wife. Treatment trials with low-dose clonazepam (0.125 mg every

Manuscript received January 24, 2000; accepted April 24, 2001.
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dysarthria and ataxia involving the trunk and extremities. MRI revealed the unchanged appearance of a 7-mm fourth ventricular nodule. His dysarthria and ataxia progressed and blurred vision developed in 1993. Neuro-ophthalmologic examination in September 1994 revealed vision of 20/20 OU with normal contrast sensitivity, color vision, pupils, confrontation visual fields, biomicroscopy, and funduscopic examination. The motility examination was notable for vertical pendular nystagmus synchronous with palatal tremor, orthophoria, and full ductions OU. Review of a 1992 MRI revealed T2 hyperintensity within the inferior olive and the dentate nucleus. There were no white matter lesions elsewhere in the brain to suggest MRI-demonstrable radiation sequelae.

Case 3
A 43-year-old woman with a past medical history of attention deficit disorder and obsessive-compulsive disorder developed a large subarachnoid hemorrhage related to the rupture of an aneurysm at the junction of the basilar and superior cerebellar arteries on April 26, 1993. Initial level of consciousness was depressed, consistent with Hunt and Hess grade III and Glasgow coma score in the 7 to 8 range. She required mechanical ventilation and intracranial pressure monitoring, and underwent ventriculostomy on April 28, 1993, for hydrocephalus. After clinical improvement, craniotomy was performed on May 19, 1993, and the aneurysm was successfully clipped as documented by a subsequent angiogram. Postoperatively, the patient noted diplopia secondary to a partial left oculomotor nerve palsy and an incongruous right superior quadrantopia. In late summer 1993, the patient developed vertical oscillopsia.

Neuro-ophthalmologic examination in September 1993 revealed oculopalatal tremor, with pendular vertical eye movements OU. Palatal region tremor persisted in sleep, according to the patient’s husband. MRI in October 1993 revealed an incidental posterior fossa arachnoid cyst, left inferior olive hyperintensity (Fig. 3), and multiple high-signal abnormalities in the white matter on T2-weighted images. Treatment with clonazepam and baclofen were successful in decreasing the oscillopsia. The patient noted the insidious onset of imbalance in the fall 1994, which progressively increased until she required a wheelchair for distance by spring 1995. MRI in November 1994 revealed unchanged high signal within the left inferior olive and bilateral high-signal lesions in the centrum semiovale. Examination revealed a wide-based ataxic gait with mild heel-to-shin and finger-to-nose difficulty. The ataxia stabilized by late 1995 and has not significantly changed with subsequent examinations to date.

**DISCUSSION**
Oculopalatal myoclonus was originally described by Spencer (2) more than 100 years ago. The term myoclonus is a misnomer when applied to these patients (1), and the palatal component has been more correctly labeled palatal tremor (3). The term symptomatic palatal
tremor has been suggested in place of oculopalatal myoclonus in order to distinguish this entity from essential palatal tremor (4–7). Our report concerns symptomatic palatal tremor; however, this term fails to identify the source of greatest distress, namely pendular nystagmus. The term oculopalatal tremor more accurately describes the clinical phenomenology in these patients.

Oculopalatal tremor occurs as a late consequence following an acute brainstem lesion after a median range of 10 to 11 months (range from 0–49 months) (8,9). Case 2 in our series represents the longest reported interval (7 years) between the initial lesion and the development of OPT.

The pathophysiologic link of OPT to the triangle connecting the dentate nucleus, the contralateral red nucleus, and the inferior olive was proposed in 1931 (10). Several theories have been advanced to explain the tardive occurrence of OPT, with more recent focus on the inferior olive as a oscillatory rhythmic generator (4,11,12). Disruption of the gamma-aminobutyric acid (GABA)-ergic system that serves to inhibit electronic coupling of inferior olive neurons may result in hypersynchronous firing, thus producing OPT (13). Positron-emission tomography scanning in patients with palatal myoclonus has demonstrated increased glucose metabolism in the inferior olive, providing a functional imaging correlate for this theory (14). Histopathologic examination of the inferior olivary nucleus in patients with OPT demonstrates enlarged vacuolated neurons and enlarged astrocytes (pseudohypertrophy, or hypertrophic degeneration) with increased acetylcholinesterase products (15,16). MRI provides a radiographic correlate for this change, typically demonstrating hyperintensity within the inferior olive, which we have referred to as the "pimento sign" (Fig. 1 and Fig. 3) (Johnstone, Personal communication) (17).

Management of OPT with anticholinergics, benzodiazepine derivatives such as clonazepam, gabapentin, scopolamine, carbamazepine, 5-hydroxytryptophan, and baclofen, have produced variable success (18–20). The patient in case 1 in our series failed to benefit from trials with several of these agents, primarily because of drug intolerance, whereas the patient in case 3 obtained visual relief from combination therapy including clonazepam and baclofen.

Sperling and Herrmann (21) described two patients in 1985 with the spontaneous onset of progressive ataxia associated with palatal myoclonus that developed in the absence of an identifiable acute brainstem lesion. One of these patients had OPT with MRI-demonstrable inferior olive hyperintensity. These patients were distinguished by the absence of an identifiable acute lesion and one patient's lack of ocular involvement. Reports by Deuschl et al. (4–6) documented delayed ataxia in association with oculopalatal tremor. These authors focused on the contrast between four patients with essential palatal tremor and six patients with symptomatic palatal tremor plus nystagmus (4). Among the six patients with symptomatic palatal tremor, two patients experienced worsening of their symptoms during the months after the acute insult (patient 9 poststroke and patient 10 after brainstem cavernoma hemorrhage). Progression was characterized as "slight" in these two patients (although at least one of the patients became wheelchair-bound). The investigators felt that this delayed progression "... suggests cerebellar dysfunction may have progressed even with a monophasic central nervous system insult" (4). Our patients confirm this late-onset ataxia as a real and potentially disabling event after the development of OPT.

The delayed onset of ataxia or movement disorders without OPT has rarely been reported weeks to years after acute lesions, including generalized hypoxic–ischemic insult, stroke, or trauma (22–26). Traumatic brain-injured patients who developed subsequent movement disorders have generally suffered more serious injuries, as evidenced by their significantly lower Glasgow coma scores on admission. The presence of generalized cerebral edema on initial CT scanning was significantly associated with the later development of movement disorders in one report (27). The association between larger initial lesion size and delayed development of neurologic sequelae in these patients parallels our experience with OPT and tardive ataxia.

Oculopalatal tremor appears to occur on a spectrum as a delayed sequel in a minority of patients after acute brainstem lesions. The emergence of tardive ataxia may represent an extreme on this clinical expression. The delayed ataxia proved to be the most disabling feature in two of our patients (from cases 1 and 2). All three of our cases, clinically and radiographically, showed large bilateral acute brainstem lesions, suggesting that such characteristics, in addition to inferior olive sparing, are prerequisites for the development of delayed ataxia with OPT. The apparent rarity of OPT with tardive ataxia may be related to these unique lesion requirements. Often patients with such large bilateral brainstem lesions die acutely or the lesion destroys the inferior olive and
Accordingly fail to develop OPT. Among the subset of patients that develop OPT, tardive ataxia may be incomplete in expression, masked by a lesion acutely involving coordination, or attributed to a new lesion such as recurrent infarction. Clinicians should be cognizant of the possibility of worsening deficits, including gait ataxia in this patient population, especially among those patients with large bilateral acute lesions.

**CONCLUSIONS**

Our three cases of OPT are distinguished by the late onset of progressive extremity and gait ataxia consistent with cerebellar system dysfunction. Case 2 is also unique because it represents the longest reported delay between the acute lesion and subsequent development of OPT (7 years). It appears that larger, bilateral, yet nonfatal acute brainstem lesions that spare the inferior olive are a prerequisite for the development of OPT with tardive ataxia.

**REFERENCES**

The Effect of Lid Elevation on the Cross-Cover Test

Michael L. Rosenberg, MD. and Martin S. Gizzi, MD. PhD

Objective: To discern the effect of manual lid elevation on muscle balance using the cross-cover test.

Materials and Methods: One hundred consecutive patients who were orthophoric in all fields of gaze were prospectively studied. A repeat cross-cover test was performed with the eyes looking down and to either side while pulling the lid ipsilateral to the abducting eye up and to either side. The presence and type of any phoria was noted.

Results: Eighty-four percent of patients and 76% of eyes developed a phoria with lifting a lid. Vertical phorias developed in 79 patients and 136 eyes, whereas horizontal phorias were seen in 51 patients and 83 eyes. In all but one case, the vertical deviation was a hyperphoria ipsilateral to the elevated lid. Horizontal deviations were esophoric in 63 eyes of 39 subjects. Induced phorias were most commonly symmetric from side to side.

Conclusions: Lifting the lid produces an iatrogenic phoria that mimics a skew or IV nerve paresis. We hypothesize that stretching the lid causes traction on the levator-superior rectus complex, thereby increasing its tone. Although it makes testing more difficult, we recommend that the lids not be manipulated while performing phoria testing.

Key Words: Strabismus—Phoria—Lids—Cross-cover.

Measuring phorias with a cross-cover test in all fields of gaze is a technique that is crucial to the evaluation and follow-up of patients with ocular motility disorders. For ophthalmologists in particular, the diagnosis of a subtle IV nerve palsy or skew deviation is most often made on the basis of such measurements. Ocular refixation movements by patients with relatively low lids can be difficult to see, especially when the eyes are infraducted and abducted. It has been our routine practice to lift the lids in order to better see the movements of the eyes in this position. We noted that, in some patients, this technique affected the measured muscle balance. We prospectively investigated the incidence of this phenomenon in a series of patients with no significant phoria on routine testing by rechecking the cross-cover test with the lid elevated. We also examined whether the direction of lid manipulation affected the change.

METHODS

All patients in the neuro-ophthalmology clinic are routinely tested with a cross-cover test in all positions of gaze. For this study, we excluded patients with any history or physical examination findings suggestive of a process that could cause an extraocular muscle problem. One hundred consecutive patients with no significant phoria when looking down and to either side during routine cross-cover testing were further tested while the lids were manipulated.

While the patient looked down and to the side, the lid of the abducted eye was gently pulled up, and then up and laterally as well as up and medially. The type of any phoria was noted in each of these positions. Testing was then repeated while the subject fixated down and to the opposite side. Care was taken to pull gently on the lid and to ensure that no external pressure was placed on the globe. Measurements were not routinely made because of the difficulties of lifting the lid and trying to manipulate a prism bar with one hand and move a paddle for the cross-cover test with the other hand at the same time.

RESULTS

Phorias developed in a striking percentage of patients. Eighty-four patients and 76% of eyes developed a phoria with lifting of the lids in at least one direction. Vertical phorias were more common and developed in 79 patients and 136 eyes, whereas horizontal phorias were induced in 51 patients and 83 eyes. In all but one case, the vertical deviation was a hyperphoria ipsilateral to the elevated lid. Four patients had the vertical phoria measured. One patient measured 2 diopters, whereas the other three patients measured 4 diopters. The horizontal deviations were mostly esophorias (63 eyes in 39 subjects) with only 13 subjects (21 eyes) showing an exophoria. The horizontal phorias did not appear to be secondary to passive movement of the globe as the same effect was often observed (e.g., esophoria) no matter which direction one pulled the lid.
TABLE 1. Phorias and lid elevation

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*The patient number is in the first column. The next three columns show the results of cross-cover testing while the subject is looking down and to the right (RT) with the lid pulled up and to the right, straight up, then up and to the left (LT). The last three columns are the cross-cover findings while the subject is looking down and to the left with the lid lifted up and to the left, straight up, then up and to the right.

**E, eso; H, hyperphoria ipsilateral to the abducting eye; O, ortho; X, exo.**

Direction of lid elevation influenced the incidence and type of phoria seen. Fifty-four eyes had a vertical phoria with the lid pulled up and out but not up and in, compared with 14 eyes with a vertical phoria while the lid was pulled up and in but not up and out. Horizontal phorias had the reverse pattern. Eleven patients (16 eyes) had phorias with the lid up and out and not up and in as opposed to 40 eyes (27 subjects) with a phoria brought out with the lids pulled up and in.

Fifty-four of the patients developed vertical phorias that were the same on right and left gaze, whereas 77 patients had symmetrical horizontal patterns. Forty-six patients were symmetric for horizontal and vertical phorias.

**DISCUSSION**

During the past decade, much has been learned regarding the physical structure of the soft tissues in the orbit...
and on the function of the extraocular muscles. It is now clear that there is an extensive system of smooth muscle and fibroelastic tissue that serves to stabilize the relative position of the muscles with the globe (1–3). This system in turn maintains the same direction of action of the muscle no matter where the eye is in the orbit.

Elevating the lid in 84% of patients had an effect on extraocular muscle tone, manifested by a marked change in muscle balance. We initially suspected that the eye was being pulled in a specific direction off of the visual axis; however, this suspicion did not explain an unchanging horizontal phoria irrespective of the direction of lid pull. Obviously, this suspicion was also not the explanation in the patient who developed a hypophoria ipsilateral to the elevated lid. It seems more likely that pulling on the lid changed the relative tone of the vertical and horizontal recti by changing the position of the fibroelastic pulleys. Because different subjects have different degrees of laxity in the pulley system and in the soft tissue attaching the lid to it, it is not surprising that lifting the lid had different effects in different subjects.

Clinically, this variance among patients has made a substantial difference in our approach to measuring phorias. The typical deviation appears to be four diopters, and this deviation was easily visible. The pattern of the iatrogenic deviation mimicked an inferior rectus weakness. Unfortunately, most patients with skewss manifest the abnormality in the same pattern. Thus, many patients thought to have a skew deviation with cross-cover may have been misdiagnosed. Anyone doing cross-cover tests in all fields of gaze should be wary of this effect and test all patients without manipulating the lids.

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Olfactory Neuroblastoma—An Unusual Presentation

Peter Cackett, BSc (Hons), MBBS, MRCOphth, and Clifford Weir, BSc (Hons), MBChB, FRCOphth

Olfactory neuroblastoma, also referred to as esthesioneuroblastoma, is a rare neuroectodermal tumor that originates from the olfactory sensory epithelium in the roof of the nasal fossa (1). The majority of patients present with chronic and progressive symptoms related to the nose or sinuses, such as nasal bleeding and persistent nasal discharge, which may have been present for years before seeking medical advice (2). The most common presenting ocular complaints include chronic periorbital pain, increased lacrimation, and visual disturbance, with diplopia being relatively infrequent at this stage (2). We report a patient with olfactory neuroblastoma who presented atypically with a brief history of diplopia, followed by rapidly progressive proptosis associated with profound uniocular visual loss.

CASE REPORT

A 23-year-old woman presented to the ophthalmology department with a 3-day history of diplopia. She also reported a 1-month history of nasal stuffiness. She had no past medical or ocular history. Clinical examination revealed visual acuities of 20/20 bilaterally, with no evidence of proptosis. Her pupil reactions were normal, and optic discs were healthy bilaterally. Ocular motility assessment showed a restriction of abduction OS. She was also found to have a nodal mass in the left upper cervical area. A computerized tomography (CT) scan was performed, which showed an extensive lesion affecting the left nasal cavity, both ethmoid sinuses, and sphenoid, left maxillary, and frontal sinuses. There was extension through the skull base into the anterior cranial fossa and laterally into the orbit where there was also evidence of retrobulbar disease.

The patient was referred to otorhinolaryngologists for nasal biopsy. Histology showed a malignant round cell tumor infiltrating the respiratory mucosa, with the tumor cells immunoreacting to the neuronal markers neuron-specific enolase (NSE), synaptophysin, and neurofilament. These appearances were believed to be consistent with the diagnosis of olfactory neuroblastoma. During the 2-week period of these investigations, the patient's vision OS deteriorated rapidly to perception of light only. This deterioration was associated with the development of marked proptosis and further limitation of ocular movements. In addition, she had a left relative afferent pupil defect and bilateral optic disc swelling. In view of this finding, an urgent neurosurgical and neuroophthalmologic opinion was sought. Magnetic resonance imaging (MRI) confirmed a large enhancing soft tissue mass probably originating in the ethmoid and sphenoid sinus regions, extending laterally into the left orbit, and displacing the muscle cone and optic nerve laterally and inferiorly (Fig. 1). The tumor extended into the brain bilaterally, occupying much of the floor of the anterior cranial fossa. There was extensive fluid within the left maxillary antrum thought to be caused by obstruction of the sinus outlet. Chest radiograph, bone marrow aspirate, cerebrospinal fluid (CSF) for cytology, and

FIG. 1. Axial magnetic resonance image showing the olfactory neuroblastoma extending into the left orbit.
bone scan results were all reported as normal. CT chest, abdomen, and pelvis results were also normal.

The tumor was thought to be inoperable, and because of the risk of permanent visual loss, the patient was urgently referred to the oncology service for chemotherapy. By this stage, she had no perception of light OS. Chemotherapy consisting of intravenous ifosfamide, vincristine, and actinomycin, combined with oral dexamethasone, was started. Within 3 days, there was an improvement in her proptosis and return of diplopia, the latter suggesting some recovery of optic nerve function. The size of the left neck node was reduced by approximately half. During the next 4 months, she received a full series of six courses of chemotherapy. By the end of this treatment period, her ophthalmic status had improved considerably. Her visual acuity was 20/20 bilaterally, with diplopia only noted on extreme left gaze associated with a slight restriction of abduction. The proptosis and optic disc swelling had resolved completely, and her pupil reactions were normal.

COMMENT

Malignant lesions of the nose and paranasal sinuses may occasionally present with ophthalmic symptoms; however, olfactory neuroblastoma, an uncommon neurogenic tumor of the olfactory region, is rarely included in the differential diagnosis. This case illustrates the importance of considering such a diagnosis even when nasal symptoms are associated with unusual presenting features such as diplopia and rapidly progressive proptosis with visual loss. It also demonstrates that in advanced cases, appropriate and prompt management with chemotherapy can result in significant recovery of visual function.

REFERENCES


Optic Neuropathy in a Patient With AIDS

Judith E. A. Warner, MD, and Kristen M. Ries, MD

We present a patient with acquired immunodeficiency syndrome (AIDS) with bilateral sequential optic neuropathies attributed to the 14484 mutation of Leber hereditary optic neuropathy (LHON). We discuss the potential interaction of the mitochondrial mutation with antiretroviral therapy and review the literature.

Key Words: Leber—AIDS—Optic neuropathy.

The differential diagnosis of visual loss in a patient with AIDS is broad, spanning from cornea to cortex and encompassing all visual structures between. The medications used in the management of the disorder, both primarily for suppression of the human immunodeficiency virus (HIV) and secondarily for the management of opportunistic infections, are increasingly effective but have significant toxicities. We present the case of a man with AIDS with bilateral sequential optic neuropathies of an unusual cause.

CASE REPORT

A 36-year-old truck driver had been human immunodeficiency virus (HIV) positive since 1991. He declined antiretroviral therapy and further care (Table 1). In November 1998, he was admitted for progressive lower extremity weakness, back pain, and urinary retention. Acute cytomegalovirus (CMV) myelopathy was diagnosed by magnetic resonance imaging (MRI) and a positive CMV polymerase chain reaction (CMV-PCR) in the cerebrospinal fluid. Results from ophthalmic examination for CMV retinopathy were normal. His viral load had increased, and his CD4 cell count diminished. In follow-up 1 month later, he was recovering well, able to walk with a cane, and was taking intravenous ganciclovir, trimethoprim/sulfamethoxazole (TMP/SMX) double strength, fluconazole, nelfinavir, combined zidovudine/lamivudine, and efavirenz.

In January 1999, without any other symptoms, he failed his driver’s license exam because of new visual loss OS. He recalled that it had been blurry for a few weeks. He saw his provider in mid-February, when he was found to be anemic with hematocrit of 16.9%. Zidovudine/lamivudine was discontinued; he received three units of packed red blood cells; and stavudine and lamivudine were started. In March 1999, he was referred for neuro-ophthalmic evaluation because of new visual loss OD. The left eye had not changed since January. He described his vision as being dim or dark, with color loss. There had been no pain with either eye’s involvement.

On examination, he was a gaunt ill-appearing man in no distress. His best-corrected visual acuity was 20/200 OD and 20/400 OS. He saw 2/13 Ishihara pseudoisochromatic color plates OD and none OS. His pupils were normal, with the exception of a left relative afferent pupillary defect. Visual fields were constricted, with central and nasal defects. External exam was normal, as was slit lamp biomicroscopy. The optic nerves were pale and atrophic bilaterally, with more pallor OS than OD. There was no evidence of past or present retinopathy.

He had smoked one to two packs of cigarettes per day for the past 10 years. He denied recreational drug use or alcohol abuse. His past medical history was notable only for the previously mentioned events, an appendectomy at age 21, and bacterial gastritis at age 24. There was no family history of blindness, although his father was reported to have poor night vision. His antiretroviral medications were stavudine, lamivudine, nelfinavir, and efavirenz, and he remained on intravenous ganciclovir, TMP/SMX, and fluconazole.

An extensive evaluation was undertaken for a compressive or infectious cause of his visual loss, including lumbar puncture. No clear cause was discovered. There was no improvement after a brief course of prednisone. Pulmonary nodules were biopsied and were found to result from Mycobacterium avium intracellulare. Two months later, he developed seizures, left hemiparesis, and depressed mental status and was found to have CMV meningoencephalitis. His anti-HIV therapy was unchanged. New CMV retinitis was discovered. His optic nerves were chalky white. Lactate was elevated at 4.5 mmol/L (normal: 0.5–2.2 mmol/L). He was able to
OPTIC NEUROPATHY IN A PATIENT WITH AIDS

leave the hospital after a protracted course but died shortly thereafter. An autopsy was not performed.

Several weeks after his death, a report of genetic testing revealed a T to C transition at the mitochondrial position 14484, compatible with the diagnosis of Leber hereditary optic neuropathy (LHON).

**DISCUSSION**

The visual loss suffered by our patient was typical for LHON, with painless severe bilateral sequential optic neuropathies occurring without remission. LHON is a maternally inherited optic neuropathy affecting primarily men in the late teens through mid-20s. It is associated with a variety of mitochondrial mutations, although not all people harboring the mutation will experience visual loss. Environmental factors that stress the body’s mitochondrial respiratory capacity may initiate phenotypic expression of the disease (1). We propose that his visual loss was caused by LHON precipitated by antiretroviral therapy.

Our patient had been HIV positive for many years, and his viral count at the time of the visual loss was relatively improved from months earlier, making it unlikely that his visual loss was a direct result of HIV infection. Although he had previously had CMV myelopathy, he was thought to be in remission, on treatment, at the time of the visual loss. He subsequently developed CMV retinitis, but this was not present until 3 months after the onset of his optic neuropathies. CMV has been associated with optic neuritis, but typically the patients have not only papillitis but also CMV retinitis (2). No other infectious causes of optic neuropathy were discovered.

Medication-related toxic optic neuropathies typically cause simultaneous involvement. Ganciclovir is not believed to be toxic to optic nerves or the central nervous system. TMP/SMX has not been reported to cause optic neuropathy. This patient was not found to be vitamin deficient and did not have compressive lesions or elevated intracranial pressure. Our patient’s visual loss occurred shortly after initiation of highly active antiretroviral therapy (HAART). The temporal association between the onset of his visual loss and the initiation of HAART suggests causation.

Luke’s letter to the editor (3) reports an HIV-positive man harboring the 11778 Leber mutation with visual loss on long-term zidovudine (AZT), a nucleoside analogue reverse transcriptase inhibitor (NRTI). The visual loss occurred 6 months after the addition of indinavir (protease inhibitor) and nevirapine (non-NRTI). This report links the occurrence of visual loss to chronic use of zidovudine. There are also several reports of a remitting optic neuropathy thought to be the direct result of HIV infection (4–6). In most of these cases, the patients were not on NRTI therapy. The exception is one of the cases presented by Newman and Lessell (6). This man was diagnosed with AIDS and placed on zidovudine 5 months before visual loss. The Leber mutation was not reported in this case, and the patient had substantial recovery of his vision—temporally associated with the initiation of prednisone—arguing against LHON as the cause.

There have been numerous reports of the NRTI zidovudine causing mitochondrial toxicity. One study demonstrated that 17% of 41 patients treated chronically with zidovudine therapy had clinical evidence of mitochondrial myopathy (7). Zidovudine is thought to cause mitochondrial toxicity in two ways. The first way is via competitive and noncompetitive inhibition of mitochondrial DNA polymerase gamma, causing mutation and depletion of mitochondrial DNA (mtDNA) and the enzymes it encodes. The second way, a result of the first, is impaired oxidative phosphorylation (8). Wang et al. (9) described depletion of normal mtDNA, and relative and absolute increase in deleted mtDNA in Kearns–Sayre syndrome fibroblasts cultured in therapeutic levels of zidovudine. Stavudine, or d4T, has been implicated in NRTI-associated lactic acidosis clinically (10) and was shown to be a more potent in vitro inhibitor of mtDNA polymerase gamma than zidovudine (11). Clinically, it can cause a peripheral axonal neuropathy (12). Lamivudine (another NRTI) is not thought to be toxic to mitochondria (13), although it has not been studied for additive effect on mitochondrial toxicity when used in combination with zidovudine, a common application. Our patient’s initial visual loss occurred several months after starting the combination drug zidovudine/lamivudine. The second eye became involved within weeks after switching to stavudine and lamivudine. All of these medications are NRTIs shown to stress oxidative phosphorylation.

Evaluation of visual loss in patients with AIDS is complex, requiring careful investigation of infectious causes. We cannot completely exclude the possibility that our patient’s optic neuropathies were caused by CMV or another infection. His CMV was thought to be in remission and other causative infections were not discovered. LHON and HIV are disorders that tend to affect younger men, so they may occur together without requiring a link. We also cannot exclude the possibility that the association of the NRTI use with the visual loss was coincidental rather than causative. The precipitation of

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**TABLE 1. Medications, CD4 count, and viral load during course of patient’s illness**

<table>
<thead>
<tr>
<th>Date</th>
<th>HAART medications</th>
<th>CD4+/CD3+ (296–1555 #/uL)</th>
<th>%CD4+/CD3+ (23–57%)</th>
<th>Viral load (HIV RNA copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>0</td>
<td>330</td>
<td>25</td>
<td>45,000</td>
</tr>
<tr>
<td>November 1996</td>
<td>0</td>
<td>61</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>December 1998</td>
<td>Zidovudine, lamivudine, nelfinavir, efavirenz</td>
<td>275</td>
<td>19</td>
<td>940</td>
</tr>
<tr>
<td>February 1999</td>
<td>Stavudine, lamivudine, nelfinavir, efavirenz</td>
<td>136</td>
<td>24</td>
<td>370</td>
</tr>
</tbody>
</table>

HAART, highly active antiretroviral therapy.
the visual loss of LHON by oxidative stress is controversial, and attempts to demonstrate the association have proven ambiguous. A recent large study failed to show an association between LHON onset and use of tobacco or alcohol (14).

We suggest that our patient lost vision because of the combination of the LHON mutation and HAART therapy with several medications known to have mitochondrial toxicity. One possibility to explain the onset of visual loss is oxidative stress induced by mitochondrial toxicity in a patient with poor reserves caused by mutated mitochondria. Another less likely explanation is an increasing proportion of mutated mitochondrial DNA compared with wild-type DNA, resulting in a threshold effect optic neuropathy. There is no current established management for LHON, but we would suggest that potent combinations of NRTIs be used with caution in patients with family histories suggestive of LHON. For patients on NRTIs experiencing monocular optic neuropathy without a clear cause, cessation of high-intensity therapy may be indicated until LHON is excluded.

REFERENCES

Primary Central Nervous System Lymphoma Involving the Optic Chiasm in AIDS

Andrew G. Lee, MD, Rosa A. Tang, MD, Dwayne Roberts, MD, Jade S. Schiffman, MD, and Anne Osborne, MD

Objective: To report visual loss resulting from chiasmal involvement by primary central nervous system lymphoma (PCNSL).

Materials and Methods: Case report.

Results: A patient with the acquired immune deficiency syndrome (AIDS) presented with visual loss resulting from PCNSL involving the optic chiasm. The clinical findings, neuroimaging, pathology, and treatment of this patient are described.

Conclusions: Although rare, clinicians should consider PCNSL in the differential of a hypothalamic/chiasmal mass, especially in a patient with AIDS.

Primary central nervous system lymphoma (PCNSL) is an uncommon intracranial lesion representing less than 0.7% of all malignant lymphomas and less than 1% of all intracranial tumors. PCNSL is more common in immunocompromised patients, such as those with acquired immune deficiency syndrome (AIDS). PCNSL typically presents as focal or multifocal lesion(s) of the cerebral hemispheres involving the basal ganglia, cortical–white matter junction, thalamus, and periventricular areas. Visual loss in PCNSL has been reported, but direct optic nerve or chiasmal involvement is rare. We report a case of PCNSL involving the optic chiasm in a patient with AIDS and review the selected English language literature (1–22).

CASE REPORT

A 42-year-old man presented with severe headaches and bilateral visual loss. Past medical history was significant for positive human immunodeficiency virus (HIV) test in December 1996 but no AIDS-defining illness. CD4 count was 209 on March 20, 1997. Medications included 400 mg of ritonavir twice daily, 400 mg of saquinavir twice daily, one Bactrim (Roche Laboratories, Nutley, NJ) daily, 150 mg of lamivudine twice daily, 40 mg of stavudine twice daily, and 100 mg of didanosine twice daily. Past ocular history was noncontributory, and results from previous eye exams were normal.

He developed the acute onset of bilateral simultaneous progressive visual loss, headache for the previous 3 weeks, and intermittent vague diplopia. On September 15, 1997, the visual acuity was 20/20 OD and 20/40 OS. Pupil, slit lamp, motility, and ophthalmoscopic exam results were normal. The visual loss continued to progress, however, and he was admitted to the hospital on September 19, 1997. At that time, he had symptoms of increased somnolence, mental status changes, fever, and chills. Ophthalmologic examination now revealed a visual acuity of hand motions OU, a bitemporal hemianopic visual field defect to confrontational testing, poorly reactive pupils OU, and optic disc edema OU. The visual loss progressed to no light perception OU.

He developed diabetes insipidus. Computed tomography (CT) scan of the head showed a suprasellar mass. Magnetic resonance imaging (MRI) of the head revealed a hypothalamic mass with homogenous enhancement and involvement of both optic nerves and the optic chiasm (Fig. 1 and Fig. 2). Right and left internal carotid artery and left vertebral artery cerebral angiogram were normal. Lumbar puncture revealed normal cerebrospinal fluid (CSF) analysis, including normal protein, cell count, and glucose levels. CSF cryptococcal antigen and CSF cytology were negative for malignancy. Immunoglobulin (Ig) G for toxoplasmosis was negative. Neurosurgery performed a right craniotomy with biopsy of the lesion. Pathology was nondiagnostic and showed only gliosis and hemorrhage but no malignancy. The patient was treated with 4 mg of intravenous dexamethasone four times daily with marginal improvement of vision. During the next few weeks, the patient’s vision continued to deteriorate, and on October 8, 1997, the visual acuity was no light perception OD and hand motion OS. The pupils were sluggishly reactive OU, and there was a right relative afferent papillary defect. Ophthalmoscopy...
A. G. LEE ET AL.

FIG. 1. Axial postcontrast T1-weighted MRI of the brain reveals a suprasellar mass with enhancement of the optic chiasm and both optic nerves (arrow).

showed optic atrophy OU. Single photon emission CT (SPECT) was normal. Stereotactic biopsy of the lesion on October 11, 1997, demonstrated monotonous sheets of lymphocytes with enlarged pleomorphic nuclei consistent with lymphoma (Fig. 3). Monoclonal antibodies against CD20 were positive for B cells and were negative for CD3 (T-cell markers). A diagnosis of primary central nervous system lymphoma was made. The patient was treated with palliative radiation therapy to the brain (30 Gy in ten fractions), chemotherapy, and dexamethasone. He was transferred to a skilled nursing facility after discharge.

FIG. 2. Coronal postcontrast T1-weighted MRI of the brain demonstrates the enhancing optic nerves bilaterally (arrow).

FIG. 3. Medium power photomicrograph of monotonous sheets of lymphocytes with enlarged pleomorphic nuclei (arrow).

DISCUSSION

Infection with HIV is associated with PCNSL, and the incidence of PCNSL has increased with the advent and spread of AIDS (1-4). The reported incidence of non-Hodgkin lymphoma in AIDS patients ranges from 2.9 to 14.5%, and it is the AIDS-defining illness in as many as 16% of cases (1-4, 8-10). Goplen et al. (10) reported 29 adult cases in 225 (19%) patients with AIDS, and 19 patients (12%) had PCNSL. PCNSL is the most common noninfectious mass lesion in AIDS and is a major threat to long-term survival in patients (fourth leading cause of death) (3,8).

Primary central nervous system lymphoma in AIDS patients may differ from those that occur in immunocompromised but non-AIDS patients. The features of PCNSL in AIDS patients include few or no neurologic symptoms, multifocal necrotic lesions, frequent association with opportunistic infections or HIV encephalitis, and B-cell origin with high-grade pathology (2). Epstein-Barr virus (EBV) has been associated with PCNSL in AIDS patients, but the exact pathogenesis of EBV in PCNSL remains to be completely defined (2). Our patient was HIV-positive.

Involvement of the optic apparatus by PCNSL is rare. Visual loss resulting from lymphoma may occur with intraocular involvement (5,6,11,12,14,17,18). The older literature referred to these intraocular cases as “reticulum cell sarcoma,” but the pathology is large B-cell lymphoma (18).

In addition, PCNSL may affect the intraorbital or intracranial optic nerves, chiasm, radiations, or visual cortex. Cavernous sinus or superior orbital fissure involvement and direct infiltrative or compressive lesion (e.g., optic nerve, chiasm, and tract) have also been reported (6,7,11,13,14,16,18,20-22). Parvin and Van Dyk (18) reported a case of PCNSL presenting as a steroid-responsive optic neuropathy with an enlarged optic nerve. Corticosteroids may cause transient clinical or ra-
diologic improvement of PCNSL, and steroid responsiveness of a lesion does not exclude lymphoma from the differential diagnosis. Bullock et al. (6) reported non-Hodgkin lymphoma invading the optic nerve in one patient. Sakai et al. (20) reported primary meningeal lymphoma presenting with visual loss resulting from a sellar/chiasmal mass. A suprasellar mass is rarely caused by focal PCNSL, and to our knowledge, our case is unique in that it was the presenting sign of lymphoma in a patient diagnosed with AIDS (16,22).

In most cases of PCNSL in AIDS, the lesions are multifocal. In our case, there was a focal suprasellar mass involving the hypothalamus and optic chiasm/nerves. The differential for such a mass includes infiltrating neoplasm (e.g., hypothalamic glioma, lymphoma), inflammatory lesion (e.g., sarcoid, granulomatous disease), or eosinophilic granuloma.

In a patient with AIDS, the most common intracranial lesions are toxoplasmosis, PCNSL, and progressive multifocal leukoencephalopathy. The neuroimaging characteristics of toxoplasmosis encephalitis and PCNSL are well described (15,19). Unfortunately, in the majority of cases (50–80%), it is not possible to differentiate the two lesions radiographically, and both may present with focal or multifocal, ring or nodular enhancing masses with surrounding edema that are located in the superficial (e.g., corticomedullary junction) or deep (e.g., basal ganglia, thalamus) cerebral hemispheres.

The MRI characteristics for PCNSL and toxoplasmosis include isointensity to gray matter on T2-weighted images. The rim of PCNSL lesions may appear isointense to gray matter on T2-weighted images with a hyperintense center. Although ring enhancement in PCNSL is common, solid enhancement may also be seen, as in our case. The suprasellar mass lesion in our case was unusual for either toxoplasmosis or PCNSL (15,19).

Although the major neuroimaging differential diagnoses for a contrast enhancing mass in a patient with AIDS are toxoplasmosis and PCNSL, other primary brain (1,4,15) neoplasms (e.g., glioblastoma multiforme) and other less common lesions should be considered (e.g., metastatic Kaposi sarcoma, herpes simplex virus, cryptococcoma, mycobacterial, Nocardia, Candida, aspergillus abscess).

Toxoplasmosis is the most frequent (50–70%) cause of a mass lesion of the brain in AIDS, and therefore many centers empirically treat for toxoplasmosis and then follow the patients with serial neuroimaging for treatment response (up to 85% response within 1 week). Patients with atypical neuroimaging characteristics or those who fail empiric antitoxoplasmosis therapy usually are considered for stereotactic biopsy to exclude tumors, including PCNSL (15).

Thallium-201 SPECT and 18F-Fluoro-2-deoxyglucose (FDG)-positron emission tomography (PET) have been proposed as imaging modalities that may allow differentiation of PCNSL from toxoplasmosis encephalitis (15,19). Our patient underwent a SPECT study that was negative; the significance of this finding is uncertain.

The histopathology of lymphoma includes large cells with scant cytoplasm, coarse nuclear chromatin, and prominent nucleoli. Cytochemical markers and immunophenotyping are able to define the cell type (B cell or T cell) and demonstrate clonality for lymphoma. Most PCNSLs are of B-cell origin, but T-cell PCNSL has also been reported (3). A higher man-to-woman ratio and a more frequent infratentorial location are seen in T-cell PCNSL (4). Our patient had a large B-cell lymphoma.

The main management of PCNSL is whole-brain radiation therapy (9). Chemotherapy may have a less prominent role for patients already immunocompromised by AIDS (3). Unfortunately, although PCNSL is radiosensitive, the prognosis is generally poor, and increased survival time is limited to months. Patients with PCNSL and AIDS often succumb to opportunistic infections. Clinicians should be aware that PCNSL in AIDS patients may present as a focal suprasellar mass with visual loss resulting from an optic neuropathy or chiasmopathy.

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The Heidenhain Variant of Creutzfeldt–Jakob Disease: Clinical, Pathologic, and Neuroimaging Findings

Dina A. Jacobs, MD, Robert L. Lesser, MD, Zissimos Mourelatos, MD, Steven L. Galetta, MD, and Laura J. Balcer, MD, MSCE

We report two patients who developed isolated visual symptoms and signs as initial manifestations of Creutzfeldt–Jakob disease (CJD). Both patients had normal conventional T1- and T2-weighted brain magnetic resonance (MR) images; in one patient, early cortical abnormalities were detected by diffusion-weighted and fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). Results from the cerebrospinal fluid assay for the 14-3-3 brain protein were also negative in one patient, despite pathologic confirmation of CJD at autopsy. The Heidenhain variant of CJD should be considered in all patients who present with isolated visual manifestations, including homonymous hemianopsia and normal conventional brain MRI. Diffusion-weighted and FLAIR MRI may demonstrate early cortical abnormalities in patients with CJD. The CSF assay for the 14-3-3 protein may be normal, even in pathologically confirmed cases.

Key Words: Heidenhain variant—Creutzfeldt–Jakob disease—MRI—Cerebrospinal fluid—Homonymous hemianopsia.

Creutzfeldt–Jakob disease (CJD) is a rapidly progressive neurodegenerative disease typically characterized by dementia, myoclonus, and periodic electroencephalogram (EEG) complexes (1–4). CJD is a transmissible spongiform encephalopathy caused by prions (proteinaceous infectious particles) (3–8). Although CJD may be transmitted iatrogenically or genetically, its occurrence is most often sporadic (3,5–8). Independent of the mode of transmission, all cases of CJD are caused by abnormalities of a single neuronal membrane protein, the prion protein (PrP) (8). According to the prion hypothesis, there is a posttranslational recruitment reaction of the normal prion protein PrP to the abnormal form PrP\textsuperscript{CJD} (5–8). This event leads to conversion of the protein conformation from an alpha-helical to a beta-pleated sheet structure (5–8). The abnormal prion protein PrP\textsuperscript{CJD} then serves as the template for the conversion of more PrP\textsuperscript{CJD} to PrP\textsuperscript{CJD}, thus creating a self-perpetuating process within the brains of affected patients (8).

Patients with the Heidenhain (occipitoparietal) variant of CJD present with isolated homonymous hemianopsia or other visual disturbances, often in the absence of specific magnetic resonance imaging (MRI), EEG, or laboratory abnormalities (1,2). Visual loss in such patients is frequently attributed initially to ischemia or to other ophthalmic disorders that may be coincidentally present. We report the neuro-ophthalmologic, neuroimaging, pathologic, and laboratory findings for two patients with the Heidenhain variant of CJD. Both patients had visual loss and homonymous field defects as initial manifestations of their disease. MRI, EEG, and cerebrospinal fluid (CSF) findings were non-specific; the second patient had an incidental pituitary adenoma whose anatomic location could not completely explain the pattern and extent of his visual loss. Diagnostic issues for patients with the Heidenhain variant of CJD, including the use of the CSF 14-3-3 protein assay, MRI techniques, and electroretinography (ERG) are also discussed.

CASE REPORTS

Case 1

In October 1997, a 79-year-old woman noted the onset of episodic colored spots in her right hemifield. The spots were described as purple in color, lasting for seconds, and initially appearing only with her eyes closed. There was no history of headache or other neurologic symptoms. The patient had recently undergone surgery for a hip fracture and since that time had begun to feel "nervous." Neuro-ophthalmologic examination and computed tomograph (CT) scan results of the brain, performed in December 1997, were normal.

In January 1998, the patient experienced two episodes of word-finding difficulty, each lasting several minutes.
She also noted that objects appeared to “shimmer” when she looked to the right. A psychiatrist had recently started the patient on sertraline for depression. Her past medical history was remarkable for hypertension.

A neuro-ophthalmologic examination, performed within days after the episodes of word-finding difficulty, revealed visual acuities of 20/25 OU. The pupils and fundi were normal. Right beating nystagmus was noted, and a right homonymous hemianopsia was present on confrontation testing. She had normal mental status, including speech, language, and memory. Mild left plantar responses were noted.

A MRI of the brain revealed normal T1- and T2-weighted images (Fig. 1A); however, increased signal intensity was demonstrated in the left parietal cortex on fluid attenuated inversion recovery (FLAIR) and diffusion-weighted images (Fig. 1B,C). Results from a carotid ultrasound and echocardiogram were within normal limits. Electroencephalogram results revealed left temporal slowing with absence of the normal alpha rhythm over the left hemisphere. Frontal intermittent rhythmic delta activity (FIRDA) was also seen. Cerebrospinal fluid (CSF) examination was unremarkable, with the exception of mildly elevated protein (60 mg/dL); CSF assay results for the 14-3-3 protein were negative. A positron-emission tomography (PET) scan of the brain revealed diffuse hypometabolism within the cerebral cortex, with an area of focal hypometabolism in the left occipital cortex (Fig. 1D).

By February 1998, the patient had experienced a rapid decline in her mental status. Myoclonus and ataxia had also developed. She frequently perseverated and had difficulty remembering her children’s names. The right homonymous hemianopsia had persisted, and visual field testing now demonstrated a left inferior quadrantanopsia. An EEG showed diffuse slowing, and the patient’s neurologic status continued to decline. The patient died at home several weeks later.

Gross pathology of the brain at autopsy was normal. Microscopic examination revealed the classic triad of histopathologic findings for CJD, including marked neuronal loss, prominent gliosis, and spongiform vacuolization within the cortical gray matter (Fig. 2). These findings were most prominently seen within the occipital cortex and to a lesser degree within the temporal lobes. A Western blot analysis of homogenized brain tissue revealed the presence of the proteinase-resistant prion protein PrPSc, confirming the diagnosis of CJD.

Case 2

A 69-year-old man presented in April 1994 with a chief complaint of “not seeing well.” He reported difficulty in seeing objects to his left side and problems with depth perception. These symptoms had progressively worsened during the preceding 6 months. There was no other history of progressive neurologic symptoms. His past medical history was significant for hypertension, which was managed with hydrochlorothiazide.

A neuro-ophthalmologic examination in April 1994 revealed visual acuities of 20/60 OD and 20/50 OS. Color vision was abnormal OU. The pupils were normal. Funduscopic examination revealed temporal pallor of the right optic disc. Goldmann visual field testing demonstrated a dense left homonymous hemianopsia; an incongruous right homonymous hemianopsia was also noted. Neurologic examination was remarkable for left hand clumsiness, mild finger-to-nose dysmetria, and left-sided hyperreflexia. Results from the MRI of the brain were normal, whereas sellar images demonstrated enlargement of the pituitary gland. Suprasellar extension of the pituitary mass was to the left side; therefore, it was thought that this finding alone could not entirely account for the patient’s visual loss, particularly the left homonymous hemianopsia. CSF examination results were normal with negative cytology.

During the next 10 days, the patient noted further loss of vision to the right OU. Examination revealed visual acuities of 20/80. He had also developed confusion and short-term memory difficulty. Biopsy of the right frontal lobe revealed spongiform vacuolization within the cortical gray matter. An EEG revealed moderate to severe slowing with bilateral occipital epileptiform discharges. The patient became progressively more confused and developed myoclonus; he died in June 1994.

Gross examination of the brain at autopsy was normal. Diffuse spongiform vacuolization, neuronal loss, and gliosis were demonstrated on microscopic pathology, similar to that demonstrated in Figure 2. Microscopic examination of the pituitary mass was consistent with a pituitary adenoma.

DISCUSSION

Although dementia, myoclonus, and ataxia are the most common clinical manifestations of CJD, our patients presented initially with isolated visual symptoms, consistent with the Heidenhain variant (1,2,10). Presenting signs and symptoms in patients with the Heidenhain variant of CJD may include visual field defects, visual hallucinations, visual agnosia, cortical blindness, and abnormal color or visuospatial perception (1,2,10). Isolated eye movement disturbances may also occur (1,11). Patients may initially complain of vague visual disturbances, and may give up reading or watching television. Purvin et al. (12) described a patient who presented with palinopsia as a presenting manifestation of CJD. Ophthalmologic examinations early in the course of CJD are often unrevealing, and patients may try new eyeglasses without resolution of symptoms (10). Despite isolated early visual symptoms, a rapid progression to dementia and death follows. Histopathologic changes characteristic of CJD, including spongiform degeneration, neuronal loss, and astrocytic gliosis, are most pronounced in the occipital lobes of patients with the Heidenhain variant (10).

The characteristic triad of dementia, myoclonus, and abnormal EEG may be lacking in as many as 25% of patients with the Heidenhain variant of CJD (13-15).
HEIDENHAIN VARIANT OF CREUTZFELDT-JAKOB DISEASE

FIG. 1. Case 1. A: Axial T2-weighted MRI demonstrating normal cerebral cortex. B: Axial FLAIR image showing abnormal signal intensity in the left parietal cortex (arrow). C: Diffusion-weighted MRI demonstrating abnormal increased signal intensity in the left parietal cortex (arrow). D: Axial PET scan of the brain showing diffuse hypometabolism throughout the cerebral cortex and an area of focal hypometabolism in the left occipital cortex (arrow).

FIG. 2. Case 1. A: Microscopic pathology of occipital cortex (hematoxylin and eosin stain, x100) demonstrating diffuse spongiform vacuolization, marked neuronal loss, and prominent gliosis (reactive astrocytes with clear nuclei [arrow]). Note the coalescence and septation of the vacuoles; these findings distinguish the spongiform changes of Creutzfeldt-Jakob disease from those found in hypoxic cerebral edema and other neurologic disorders. Also note the presence of small vacuoles in the neuropil. B: Glial fibrillary acidic protein stain (x200) for astrocytes demonstrating prominent gliosis and reactive astrocytes (arrow) in the occipital cortex.
The classic EEG finding of 1 cycle/second triphasic waves may not be present until late in the disease. Short of brain biopsy, testing to confirm the diagnosis of CJD with certainty before death is lacking. The spinal fluid assay for the 14-3-3 protein may be a useful marker for the disease (16) but may be negative in some patients with pathologically confirmed CJD (as in case 1). The 14-3-3 assay also lacks specificity for CJD and may be positive in patients with other conditions causing neuronal death, such as stroke, hypoxic-ischemic injury, and herpes encephalitis (16). In addition, a recent report of three cases indicates that there may be false-negative results (consistent with case 1) and false-positive results for the 14-3-3 assay in patients with CJD (17).

Our cases emphasize the need for suspicion of CJD (Heidenhain variant) in patients with apparently isolated visual symptoms or field defects and normal conventional neuroimaging studies, or in cases in which MRI abnormalities (as in case 2) do not completely explain the extent of visual loss. The brain parenchyma of both patients in this series appeared normal by conventional T1- and T2-weighted MRI. Early cortical abnormalities were detected in patient 1 by diffusion-weighted and FLAIR imaging. A recent study has shown that diffusion-weighted MRI may indeed be helpful in confirming early suspicion of CJD based on the demonstration of cortical lesions (13). Although conventional MRI may show cortical and basal ganglia abnormalities on T2- and proton density-weighted images, such scans may be normal in as many as 21% of patients in the early course of CJD (15). Gadolinium enhancement is most often absent (15). Diffusion-weighted imaging may be abnormal secondary to cell lysis and membrane disruption (13). Diffusion-weighted imaging and FLAIR sequences should therefore be included in MRI protocols for patients with unexplained visual loss and normal T1- and T2-weighted images.

Recent reports have suggested that the ERG may also provide a useful adjunct in cases of suspected CJD (18,19). Patients with CJD have been demonstrated to have a decrease in the b-wave amplitude of the ERG (18,19). This abnormality most likely relates to degenerative changes in the outer plexiform layer and Mueller cells (18-20). Whereas a decrease in the b-wave amplitude is not specific for CJD, the magnitude of this finding may correlate with disease progression (18). Richard et al. (21) reported progressive reduction in the b-wave amplitude in two patients with CJD during the course of their disease (21). ERG abnormalities may appear before the emergence of characteristic EEG findings in CJD (21), particularly among patients with visual symptoms.

The Heidenhain variant of CJD must be considered in all patients who present with isolated visual complaints and either normal conventional brain neuroimaging or findings that do not completely correlate with signs and symptoms. In such patients, diffusion-weighted and FLAIR MRI may reveal early cortical changes (13,15). CSF assay for the 14-3-3 protein, if positive, may also aid in the diagnosis for patients in whom the degree of suspicion for CJD is high (16).

REFERENCES

Optic Neuropathy and Central Retinal Artery Occlusion in Non-Hodgkin Lymphoma

Anna B. Fierz, MD, Sabine Sartoretti, MD, and Adelheid M. Thoelen, MD

We report a patient with systemic large cell non-Hodgkin lymphoma in remission who presented with the rare combination of optic neuropathy and central retinal artery occlusion. Another unusual feature of this case is the lack of enhancement in the affected region on magnetic resonance imaging only hours after the first dose of steroids. Despite prompt treatment with steroids and radiotherapy, lymphomatous infiltration of the meninges developed 2 months later and was ultimately fatal.

Key Words: Central retinal artery occlusion—Magnetic resonance imaging—Non-Hodgkin lymphoma—Optic neuropathy—Infiltrative.

Optic nerve infiltration is a rare but well-recognized complication of non-Hodgkin lymphoma (NHL). Rarely, retinal vascular occlusions (arterial or venous or both) may also occur in NHL. We report a case of combined optic neuropathy and central retinal artery occlusion (CRAO) in a patient in apparent NHL remission.

CASE REPORT

In March 1999, a 75-year-old woman was investigated for hyperparathyroidism and diagnosed with an aggressive form of NHL (IWF group H) with a focus in the parathyroid gland. Staging revealed additional lesions in the spine and supraclavicular lymph nodes. After four cycles of chemotherapy, she was considered to be in remission. On the evening of July 31, 1999, she suffered visual loss OD, progressing to blindness overnight. On August 1, 1999, visual acuity OD was no light perception and there was marked disc edema with some hemorrhages. There were no vitreous cells. Systemic workup did not suggest giant cell arteritis, and erythrocyte sedimentation rate was 18 mm/h. Computed tomograph (CT) scan showed slight thickening of the retrobulbar nerve without enhancement. A presumptive diagnosis of non-arteritic anterior ischemic optic neuropathy was made, and aspirin was started. The next day, disc edema had markedly progressed. There was now also conjunctival chemosis OD, lid swelling, proptosis of 2 mm, reduced supraduction, retinal ischemia with a preserved cilio-retinal vessel, and venous engorgement and hemorrhages temporal to the fovea, suggesting CRAO and accompanying venostasis retinopathy (Fig. 1). Fluorescein angiography confirmed CRAO OD with a spared cilio-retinal artery (Fig. 2). Oral prednisone, 100 mg daily, was started on August 2, 1999. Magnetic resonance imaging (MRI) done on August 3, 1999, revealed thickening and hyperintensity of the right retrobulbar optic nerve reaching almost to the chiasm, consistent with ischemia, but no clear enhancement (Fig. 3). Despite this finding, lymphomatous infiltration was suspected. The patient refused a lumbar puncture. During treatment with prednisone and irradiation of the right orbit with 7x3 Gy, swelling and proptosis resolved, and motility returned to normal, but the eye remained blind. Follow-up MRI 2 weeks later was essentially unchanged. Marked optic atrophy OD developed. In October 1999, lymphomatous infiltration of the meninges was diagnosed, and the patient died in January 2000. No autopsy was performed.

DISCUSSION

Large cell non-Hodgkin lymphoma is the most common type of lymphoma involving the eye and the central nervous system (1). The primary oculocerebral forms of NHL were formerly known as reticulum cell sarcoma, but histologically similar types of NHL can originate in other locations (commonly lymph nodes or the intestinal...
FIG. 1. Fundus OD on August 2, 1999. Disc edema and central retinal artery occlusion with a preserved cilioretinal vessel and a few hemorrhages, despite retinal ischemia, are visible.

FIG. 2. Fluorescein angiography OD on August 2, 1999, after 41 seconds.

FIG. 3. T2-weighted MRI of the brain and orbits on August 3, 1999, showing thickening and hyperintensity of the right optic nerve up to the orbital apex.

tract) and spread to the orbit. There have been several reports of optic neuropathy in NHL, including in patients in remission (2). As in our patient, the optic neuropathy may be accompanied by signs of a retrobulbar mass, such as proptosis and impaired motility (3). Central retinal vessel occlusion is distinctly unusual in this setting but can occur with or without optic nerve involvement. Saatci et al. (4) reported a combined CRAO and vein occlusion with disc edema in a 14-year-old boy. Gayer et al. (5) described the combination of CRAO and optic neuropathy in a terminally ill NHL patient with sepsis; the CRAO was presumed to be caused by septic emboli.

In our patient, it remains unclear whether the optic nerve itself was infiltrated or whether infiltration of the surrounding tissue led to an ischemic neuropathy. The lesion could not be localized even on MRI, which showed a hyperdense optic nerve on T2-weighted images but no enhancement—neither in the nerve nor in the orbit—such as that usually found with lymphoma. This finding may be the result of the first dose of steroids given 15 hours before imaging, but nonenhancement (in immunocompetent patients) has been reported in primary central nervous system non-Hodgkin lymphoma (6). Clinically, visual loss is usually less rapid and profound with infiltration of the nerve only, and some cases have been reported to improve with steroids or irradiation (2,3). We therefore believe that the central retinal artery was occluded early, possibly because of direct infiltration at the level of the disc. The development of concomitant venostasis retinopathy is evidence of a comparatively slow occlusion of the artery that permitted a residual perfusion. Because we have no pathology, we cannot rule out that visual loss was caused by another process, e.g., ischemia alone. However, ischemia would fail to explain the signs of a retrobulbar mass, which accompanied the CRAO. The clinical course during the next few months is also classic for lymphomatous infiltration of the orbit and optic nerve, which frequently heralds spread to the central nervous system. This case demonstrates that a high index of suspicion is required when managing high-grade NHL. Despite the sophisticated imaging techniques available today, clinical judgment remains the key to the correct diagnosis.
REFERENCES


Case Report

Postpartum Pituitary Hypophysitis

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The case of a young woman who developed lymphocytic hypophysitis 2 weeks after delivery of a healthy baby is reported. The patient presented with clinical features suggestive of a pituitary mass lesion, but surgery was avoided when other clinical and radiologic features were considered. The patient recovered with steroid treatment only. We review the literature on this increasingly recognized condition and argue that medical management may be more suitable than previously thought.

Key Words: Lymphocytic hypophysitis—Pregnancy—Steroid treatment.

Inflammatory growths in the area of the pituitary gland should be considered in the preoperative differential diagnosis of every pituitary tumor that is not associated with important hormonal dysfunction, particularly in the peripartum period. It may also present in the early stages of pregnancy, with symptoms mimicking hyperemesis gravidarum or meningeal irritation (1). Hypophysitis has been reported in men and in association with a number of autoimmune diseases, including Sjogren syndrome, Graves disease, diabetes, and rheumatoid arthritis.

The precise etiology remains unclear, but animal studies have shown that rubella virus glycoproteins can induce autoimmune lymphocytic hypophysitis in Syrian hamsters and that neonatal thymectomy prevents the disease (2). A definitive diagnosis can be made by endoscopic endonasal biopsy (3), but we suggest that histologic examination may not always be necessary to diagnose hypophysitis when characteristic clinical features are found, as illustrated by the present case.

CASE REPORT

A twenty-year-old right-handed woman presented with a week-long history of progressive bilateral visual deterioration in early January 2000. During the previous week, she had given birth to a baby girl by Caesarean section. Initially, she noticed visual blurring, particularly in the temporal fields of vision, when she moved her head quickly. She also began to complain of vague frontotemporal headaches without diurnal variation or change with posture. There was no nausea, vomiting, diplopia, or ocular pain. She had no other symptoms. At presentation, she had not begun to lactate. The pregnancy had been uneventful, and before conception, her menstrual cycle had been regular. She had a miscarriage 3 years previously. There was no other relevant past medical history and no family history of relevance—in particular, no past or family history of autoimmune disease.

On examination, her visual acuity was 6/12 OD and 6/9 OS. There was a bitemporal hemianopia on field testing with normal fundus examination. There were no other abnormal neurologic or endocrinologic signs. A computed tomograph (CT) scan was reported as showing a pituitary macroadenoma extending into the suprasellar region. Routine hematology tests revealed a hemoglobin level of 10.7 g/dL, an increased platelet count of 436, and a normal biochemical profile. Her prolactin level was normal (149 nmol/L), but her morning Cortisol level was low at 27 U/L (normal, 170–720 U/L); the low Cortisol level may have been influenced by the steroids being used in her treatment. Her thyroxine level was low (< 6.4), but her thyroid-stimulating hormone level and bone profile were normal.

Before and after contrast, T1-weighted magnetic resonance images (MRI) showed a homogeneously enhancing pituitary mass with suprasellar extension compressing the optic chiasm and the hypothalamus (Fig. 1). The mass was intimately related to, but not surrounding, the cavernous and supraclinoid internal carotid arteries. No intracavernous extension or evidence of hemorrhage was noted. She was given 4 mg of dexamethasone four times daily for a presumed diagnosis of lymphocytic hypophysitis. During the first 3 days of treatment, her headaches improved, and her visual acuity improved to 6/4 bilaterally. There was mild red desaturation in the temporal field OU, indicating marked improvement in visual fields. Cortisol and thyroxine replacement was begun.
A second MRI scan was performed 4 days after the first imaging study (Fig. 2). The homogenous enhancement around the pituitary gland had reduced considerably and was now clear of the optic chiasm. She was discharged on a reducing dose of dexamethasone and replacement thyroxine and hydrocortisone therapy. On the day of discharge, her visual function was normal, including normal fields, visual acuity, and color vision.

**DISCUSSION**

Our patient represents a classic example of this unusual condition, the etiology of which remains unknown.

She displayed features of a suprasellar lesion, and the clinical context and imaging findings suggested lymphocytic hypophysitis. These clinical features include a rapid onset of visual impairment, often in the peripartum period (4). CT and MRI imaging show a diffuse pituitary mass and enlarged pituitary stalk with homogenous contrast enhancement. Diabetes insipidus and persistent amenorrhea may occur; later, panhypopituitarism may also occur. Dynamic MRI has been used to demonstrate an abnormality of the hypophysial vasculature, even if the pituitary disease is seen to regress on conventional MRI studies (5). Gallium-67 scintigraphy may show abnormal uptake in the lesion (6). Autoantibodies to human pituitary cytosol proteins have been detected in as many as 70% of patients with biopsy-proven lymphocytic hypophysitis (7) and may represent markers for an immunologic process affecting the pituitary gland. As many as 25% of patients may have autoimmune thyroiditis (8).

Histologic examination of the pituitary shows a lymphoplasmacytic infiltrate with occasional neutrophils, eosinophils, and macrophages. There may be focal or diffuse adenohypophysial destruction of variable severity with associated fibrosis.

Most reported cases have been managed surgically, but steroid therapy has been advocated (9). One prospective study of nine patients with lymphocytic hypophysitis treated with high-dose methylprednisolone pulse therapy demonstrated improvement of adenohypophysial function in four patients. There was also a cessation of diabetes insipidus in all four patients (10). The presumptive noninvasive diagnosis of lymphocytic hypophysitis seems possible in a high proportion of patients, and high-dose steroids may result in improvement of clinical, endocrinologic, and MRI findings. In the absence of a visual field defect, however, it has been recommended that surgery and steroid therapy be withheld with periodic reassessment (11). In the absence of a controlled clinical trial, it is possible only to speculate whether there is a higher incidence of panhypopituitarism after surgery for this condition. The current report illustrates that the response to steroids may be so rapid that very little time is lost if the diagnosis is incorrect. The major differential diagnosis includes other pituitary adenomas common in pregnancy: meningiomas (which may be distinguished from this condition by imaging characteristics) and neurosarcoïdosis (the initial management of which is the same as the management for lymphocytic hypophysitis).

The natural history of lymphocytic hypophysitis begins with enlargement of the pituitary secondary to inflammatory infiltration and progresses to atrophy of the gland with destruction of pituitary tissue and replacement with fibrosis. The prognosis of the condition remains unclear, and there are only a few reports of pregnant women who have had an episode of lymphocytic hypophysitis (11). Recurrence after 2 years has also been reported (12).

REFERENCES

Interferon-Alpha 2a Treatment of Neuro-Behcet Disease

John C. Nichols, MD, Akgun Ince, MD, Levent Akduman, MD, and Eric S. Mann, MD, PhD

Behcet disease is a multisystemic, chronic, recurrent inflammatory disorder characterized as a triad of hypopyon uveitis, oral aphthae, and genital ulcers. Neurologic involvement in Behcet disease (neuro-Behcet) is common. Neuro-Behcet disease typically manifests late after disease onset, rarely coincides with ocular involvement, and often heralds a poor prognosis for final vision and survival. We present a case of neuro-Behcet disease with neurologic onset concomitant with systemic and ocular involvement that was responsive to treatment with interferon-alpha 2a.

Key Words: Interferon-alpha 2a—Behcet disease—Neuro-Behcet disease.

CASE REPORT

A 25-year-old man was referred to us because of his 2-week history of painful oral and genital ulcers. The patient denied any similar episode in the past or travel outside the United States. Although the patient was born in the United States and does appear Semitic, he denies any Japanese, Asian, or Mediterranean ancestry. Before the onset of aphthous ulcers, he reported transient blurred vision, headache, and fever.

Ocular examination revealed visual acuity 20/25 OU. Confrontation visual fields were full to finger counting. Pupils appeared normal with no relative afferent pupillary defect. There was bilateral iridocyclitis without hypopyon and trace vitreitis OU. Optic nerve examination revealed bilateral disc edema (Fig. 1) without spontaneous venous pulsations. Indirect ophthalmoscopy revealed retinitis and retinal vasculitis in the midperiphery OU.

Dermatologic evaluation upon hospital admission revealed papulopustule lesions and folliculitis on his back. The patient exhibited pathergy with pustule formation at the site of an intravenous catheter placement. Subsequent biopsy of this site demonstrated a leukocytoclastic vasculitis by histopathology. Although the results from a formal pathergy test were negative, skin manifestations were consistent with Behcet disease.

The patient had a generalized tonic-clonic seizure upon hospitalization. A magnetic resonance imaging (MRI) scan of the brain showed a right temporal lobe lesion (Fig. 2). An electroencephalogram confirmed the focus of the seizure in the right temporal lobe. A lumbar puncture was performed with an opening pressure of 21.6 cm of H₂O. The cerebral spinal fluid (CSF) revealed a lymphocytosis (white blood cells, 58/mm³ with 99% lymphocytes) and elevated protein at 50 mg/dL. A subsequent magnetic resonance venogram (MRV) performed at 6 weeks showed no dural sinus thrombosis.

Extensive laboratory evaluation for infectious etiologies, collagen vascular disease, and occult malignancy was unremarkable. Syphilis serology, human immunodeficiency virus (HIV), acute and convalescent antibody titers in the serum and CSF, and polymerase chain reaction of the CSF revealed no detection of herpes virus infection. Bacterial and viral cultures of the throat, CSF, blood and genital lesions were negative.

Interferon-alpha 2a (9 million units administered subcutaneously three times per week for 5 weeks; total dose approximately 135 million units) and colchicine (1.2 mg/day) were initiated with retinitis, and retinal vasculitis resolved at 2 weeks. Neurologic manifestations markedly improved as the temporal lobe lesion improved (evidenced by MRI scan), and disc edema nearly resolved at the 6-week follow-up. A repeat MRI scan of the brain and ocular examination at approximately 3 months showed resolution of the temporal lobe lesion (Fig. 3), disc edema, intraocular inflammation and systemic manifestations. The patient remains without systemic, ocular, and neurologic manifestations through the 8-month follow-up period, maintained only on colchicine (1.2 mg/day).

Comment

Current immunosuppressive therapy of ocular and neurologic manifestations of Behcet disease may lack efficacy (1), cause neurotoxicity, or accelerate the development of central nervous system (CNS) manifestations.
These signs and symptoms resemble those of patients with neuro-Behcet disease. Alternative therapeutic agents are thus necessary to manage this leading cause of mortality and morbidity in Behcet disease.

Interferon has antiviral, immunomodulatory, antiproliferative, and antitumoral properties. Interferon-alpha 2 treatment of Behcet disease in the absence of ocular or neurologic symptoms has been described (4). Recently prophylaxis (5) and treatment (6) of the ocular manifestations of Behcet disease have been reported with interferon-alpha 2. This report describes resolution of ocular, systemic, and neurologic manifestations of Behcet disease.
disease concurrent with interferon-alpha 2 treatment. The efficacy of interferon in the management of Behcet disease may occur through resolution of pathologic cytokinemia and endothelial disturbance found in this disease.

Neurologic involvement in Behcet disease is present in 5.3 to 25% of patients, depending on the geographic region studied (7). Clinical patterns of neuro-Behcet disease include parenchymal and nonparenchymal CNS involvement (8). Secondary or nonparenchymal CNS patterns include aseptic meningitis and bilateral disc edema without intracranial hypertension (8), as found in our patient. The presence of bilateral disc edema without dural sinus thrombosis by MRV at 6 weeks and MRI scrutinized at diagnosis emphasizes that nonparenchymal neuro-Behcet may occur in the absence of vascular involvement. A focal inflammatory lesion within the temporal lobe is atypical for parenchymal lesions in neuro-Behcet disease. Parenchymal lesions are more commonly found in the midbrain and brain stem (7). The occurrence of both patterns of CNS involvement in this patient in the absence of dural sinus thrombosis supports a similar pathogenic mechanism for each.

Criteria (9,10) establish the diagnosis of Behcet disease in this case because other diseases were excluded by diagnostic testing. Polymerase chain reaction and antibody testing for herpes viruses in the CSF and serum exclude herpetic meningoencephalitis as an alternative diagnosis. The resolution of ocular, systemic, and CNS manifestations concurrent with interferon-alpha 2a therapy is suggestive of a causative effect of treatment, and spontaneous improvement was unlikely given the typically progressive nature of neuro-Behcet disease without therapy. Controlled randomized studies are warranted to demonstrate efficacy of interferon-alpha 2a treatment of ocular and neurologic manifestations of Behcet disease.

REFERENCES

Neuro-Ophthalmic Manifestations of Head Trauma

Gregory P. Van Stavern, MD, Valérie Biousse, MD, Michael J. Lynn, MS, Deborah J. Simon, MD, and Nancy J. Newman, MD

Objective: To describe the neuro-ophthalmic findings in a group of patients with head trauma.

Materials and Methods: A retrospective chart review of all patients given a diagnosis code of head trauma in the neuro-ophthalmology unit at Emory University between 1991 and 1999.

Results: A total of 326 consecutive patients were reviewed (203 [63%] men and 123 [37.0%] women). Age ranged from 2 to 86 years, with a mean of 30 years. Motor vehicle accident was the most common cause of head trauma, occurring in 195 (59.8%) patients. An abnormal neuro-ophthalmic examination was noted in 185 of 326 patients (56.7%). Loss of consciousness was not associated with any outcome, but the presence of a neuroimaging abnormality, particularly intracranial hemorrhage, was significantly associated with specific neuro-ophthalmic deficits.

Conclusions: Head trauma causes a number of neuro-ophthalmic manifestations. The afferent and efferent pathways are vulnerable to traumatic injury, although the efferent system is more commonly affected. Loss of consciousness may not be a reliable predictor of specific neuro-ophthalmic outcomes, but neuroimaging abnormalities may.

Key Words: Neuro-ophthalmology—Head trauma—Diplopia—Visual loss.

Neuro-ophthalmic deficits may commonly follow head trauma (1–13). The afferent and efferent visual systems are susceptible to injury from a variety of mechanisms. These patients can be a diagnostic and therapeutic challenge, in large part secondary to the frequently vague nature of their visual complaints and their coexistent neurologic deficits. Although the association between head trauma and neuro-ophthalmic deficits is clear, there is as yet no definite consensus regarding the relative frequency of specific neuro-ophthalmic deficits, both afferent and efferent, that may accompany head trauma. In this review of all head trauma patients seen in one academic neuro-ophthalmology unit during a 9-year period, we determined the relative frequency of various neuro-ophthalmic deficits incurred after head trauma and their relationship to the nature of the head injury.

METHODS

A retrospective chart review of all consecutive patients seen between 1991 and 1999 in the neuro-ophthalmology unit at Emory University and given a diagnosis code of head trauma was performed. All patients underwent a standardized neuro-ophthalmic history and examination. Visual fields were tested using a Goldmann perimeter or a Humphrey automated perimeter. Length of time from injury to examination, type of trauma sustained, extent of injuries (including neuroimaging, if available), and loss of consciousness were noted for each patient. For patients diagnosed with optic neuropathy, a distinction among mechanisms of injury (indirect, direct, papilledema) was made on the basis of visual acuity, visual field, and optic disc appearance. Cause of injury, sex, loss of consciousness, and the presence of a neuroimaging abnormality were all evaluated as potential predictors of outcome, with outcome being defined as the presence of a neuro-ophthalmic deficit or a combination of neuro-ophthalmic deficits. All predictors and outcomes were categorical in nature. The association between the predictors and outcomes was evaluated using a chi-squared test. In addition to univariate analyses, multivariate analyses were done using logistic regression; however, these analyses did not reveal any important associations beyond those discovered with the univariate analyses.

RESULTS

Three hundred and twenty-six patients were reviewed. They included 203 (62.3%) men and 123 (37.7%) women. Age ranged from 2 to 86 years, with a median of 30 years. Most patients were admitted in the rehabilitation service at the time of their evaluation in our unit. The neuro-ophthalmic examination was part of a systematic evaluation obtained before their...
discharge from rehabilitation and included both symptomatic and asymptomatic patients. Only patients cooperative enough to perform a complete neuro-ophtalmic examination, including formal visual field testing, were evaluated.

The various causes of head trauma in this series are listed in Table 1. Motor vehicle accident (MVA) was the most common cause of head trauma, occurring in 195 patients (59.8%). Of these, 166 were passengers or drivers, and the remaining patients were pedestrians struck by a moving vehicle. Falls, motorcycle accidents, and projectile injuries were less common, accounting for 31.2% of patients in total. Time from injury to examination ranged from 3 days to 12 years, with a mean of 73.5 days ± 291.8 days. One hundred and thirty patients (39.9%) experienced a loss of consciousness lasting from several minutes to a prolonged coma of several months' duration (Table 2) at the time of injury. Clinically relevant neuroimaging findings at the time of injury were noted in 153 patients (46.9%) (Table 2). We considered the following abnormalities as clinically relevant: intracranial hemorrhage (ICH) (epidural, subdural, or intraparenchymal), basal skull fracture, and radiographically evident contusion. ICH was the most common finding, occurring in 185 patients (56.7%) (Table 3). Of the patients neuroimaging was normal.

An abnormal neuro-ophtalmic examination was found in 185 patients (56.7%) (Table 3). Of the patients with abnormal neuro-ophtalmic examinations, 93 (50.2%) had afferent pathway deficits, and 109 patients (58.9%) had efferent pathway deficits. Among afferent deficits, retrochiasmal visual field defects were the most common, occurring in 47 patients (50.5%). Optic neuropathies occurred in 40 patients (43%) and included indirect optic nerve injury (27.9%) and optic nerve injury secondary to previously elevated intracranial pressure with papilledema (15%). Chiasmal injury and Terson syndrome were uncommon, each occurring in three patients (3.2%). Among efferent deficits, ocular motor cranial nerve abnormalities predominated, with 84 patients (77.1%) having at least one ocular motor nerve palsy. Among these patients, 19 (22.6%) had multiple ocular motor nerve palsies. Trochlear nerve palsy was the most common deficit (51.2%), followed closely by oculomotor nerve palsy (46.4%). Twenty-four patients had bilateral ocular motor palsies, with bilateral trochlear nerve palsy occurring most frequently. Supranuclear ocular motor deficits were less common and included convergence insufficiency (16 patients, 14.7%), supranuclear gaze palsy (two patients), and dorsal midbrain syndrome (two patients). Horner syndrome was uncommon, occurring in only three patients (2.7%). Central vestibular nystagmus was documented in only two patients.

Cause of injury was not significantly associated with any outcome. Female sex was significantly associated with trochlear nerve palsy ($\chi^2 = 3.80, P = 0.05$) but not with any other outcome. Male sex was not significantly associated with any outcome. The presence of any neuroimaging abnormality was significantly associated with indirect optic nerve injury ($\chi^2 = 3.68, P = 0.05$) and oculomotor nerve palsy ($\chi^2 = 3.79, P = 0.05$).

The presence of an ICH was significantly associated with oculomotor nerve palsy ($\chi^2 = 8.86, P = 0.003$) and bilateral trochlear nerve palsy (Fisher test, two-tail, $P = 0.02$). The presence of a basilar skull fracture was significantly associated with trochlear nerve palsy (Fisher test, two-tail, $P = 0.05$). The presence of a radiographically evident contusion was not significantly associated with any outcome.

### TABLE 1. Cause of head trauma

<table>
<thead>
<tr>
<th>Cause of injury</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor vehicle accident</td>
<td>195/326 (59.8)</td>
</tr>
<tr>
<td>Passenger/driver</td>
<td>160/195 (81.5)</td>
</tr>
<tr>
<td>Pedestrian</td>
<td>29/195 (14.9)</td>
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<tr>
<td>Fall</td>
<td>38/326 (11.7)</td>
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<tr>
<td>Motorcycle accident</td>
<td>22/326 (6.7)</td>
</tr>
<tr>
<td>Struck by projectile</td>
<td>22/326 (6.7)</td>
</tr>
<tr>
<td>Gunshot wound to head</td>
<td>4/326 (1.2)</td>
</tr>
<tr>
<td>Airplane crash</td>
<td>4/326 (1.2)</td>
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<tr>
<td>Blunt injury</td>
<td>3/326 (&lt; 1)</td>
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</table>

### TABLE 2. Associated findings

<table>
<thead>
<tr>
<th>Associated findings</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of consciousness</td>
<td>196/326 (60.1%)</td>
</tr>
<tr>
<td>Present</td>
<td>130/326 (39.9%)</td>
</tr>
<tr>
<td>Neuroimaging findings</td>
<td></td>
</tr>
<tr>
<td>Significant neuroimaging</td>
<td></td>
</tr>
<tr>
<td>abnormality</td>
<td>153/323 (47.3%)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>95/153 (62.1%)</td>
</tr>
<tr>
<td>Skull fracture</td>
<td>37/153 (24.2%)</td>
</tr>
<tr>
<td>Contusion</td>
<td>44/153 (28.7%)</td>
</tr>
</tbody>
</table>

### TABLE 3. Frequency of neuro-ophtalmic deficits

<table>
<thead>
<tr>
<th>Deficits</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neuro-ophtalmic deficit</td>
<td>185/326 (55.7)</td>
</tr>
<tr>
<td>Afferent pathway deficit</td>
<td>93/153 (59.2)</td>
</tr>
<tr>
<td>Terson syndrome</td>
<td>3/93 (3.2)</td>
</tr>
<tr>
<td>Optic neuropathy</td>
<td>40/93 (43.0)</td>
</tr>
<tr>
<td>Indirect injury</td>
<td>26/93 (27.9)</td>
</tr>
<tr>
<td>Secondary</td>
<td>14/93 (15.0)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>13/93 (13.2)</td>
</tr>
<tr>
<td>Chiasmal injury</td>
<td>3/93 (3.2)</td>
</tr>
<tr>
<td>Retrochiasmal visual field defects</td>
<td>47/93 (50.5)</td>
</tr>
<tr>
<td>Efferent pathway deficit</td>
<td>109/185 (58.9)</td>
</tr>
<tr>
<td>Oculomotor nerve palsy</td>
<td>84/109 (77.1)</td>
</tr>
<tr>
<td>Cranial nerve III palsy</td>
<td>39/84 (46.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3/39 (7.7)</td>
</tr>
<tr>
<td>Cranial nerve IV palsy</td>
<td>43/84 (51.2)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>14/43 (32.5)</td>
</tr>
<tr>
<td>Cranial nerve VI palsy</td>
<td>21/84 (25.0)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>7/21 (33.3)</td>
</tr>
<tr>
<td>Multiple ocular motor nerve palsies</td>
<td>19/84 (22.6)</td>
</tr>
<tr>
<td>Convergence insufficiency</td>
<td>16/109 (14.7)</td>
</tr>
<tr>
<td>Supranuclear gaze palsy</td>
<td>2/109 (1.8)</td>
</tr>
<tr>
<td>Dorsal midbrain syndrome</td>
<td>2/109 (1.8)</td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>3/109 (2.7)</td>
</tr>
<tr>
<td>Central vestibular nystagmus</td>
<td>2/109 (1.8)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
</tr>
<tr>
<td>Jacobs et al.</td>
<td>1986</td>
</tr>
<tr>
<td>Kowal (10)</td>
<td>1992</td>
</tr>
<tr>
<td>Leprone (11)</td>
<td>1995</td>
</tr>
<tr>
<td>Mariak et al.</td>
<td>1997</td>
</tr>
<tr>
<td>Moster et al.</td>
<td>1998</td>
</tr>
<tr>
<td>Vaa Stavern et al.</td>
<td>2000</td>
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</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>M/W</th>
<th>Number of patients</th>
<th>Patient population</th>
<th>Age range (mean yrs)</th>
<th>Time from injury to exam</th>
<th>Most common cause of head injury</th>
<th>Most common afferent deficit</th>
<th>Most common efferent deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs et al.</td>
<td>21/441</td>
<td>2.6%</td>
<td>18/441, 15.9%</td>
<td>Retinal VF defects</td>
<td>29/441, 6.6%</td>
<td>4/441, 4.6%</td>
<td>3/441, 0.6%</td>
<td>19/441, 10.9%</td>
<td>2/441, 0.4%</td>
</tr>
<tr>
<td>Kowal (10)</td>
<td>1992</td>
<td>M = 161</td>
<td>20/161, 25.3%</td>
<td>Cranial nerve III palsy</td>
<td>39/161, 24%</td>
<td>2/161, 1.2%</td>
<td>1/161, 0.6%</td>
<td>3/161, 1.9%</td>
<td>1/161, 0.6%</td>
</tr>
<tr>
<td>Leprone (11)</td>
<td>1995</td>
<td>M = 32</td>
<td>2/32, 6.2%</td>
<td>Cranial nerve IV palsy</td>
<td>9/32, 28.1%</td>
<td>2/32, 6.3%</td>
<td>1/32, 3.1%</td>
<td>5/32, 15.6%</td>
<td>2/32, 6.3%</td>
</tr>
<tr>
<td>Mariak et al.</td>
<td>1997</td>
<td>M = 3</td>
<td>1/3</td>
<td>17 head trauma pts deceased within 72 hrs of injury</td>
<td>28-83</td>
<td>0-72 hours</td>
<td>MVA 11/12, 91.7%</td>
<td>Not assessed</td>
<td>Cranial nerve III palsy (6/12, 50%)</td>
</tr>
<tr>
<td>Moster et al.</td>
<td>1998</td>
<td>M = 46</td>
<td>161</td>
<td>Head trauma patients referred from rehab</td>
<td>Not provided</td>
<td>Not provided</td>
<td>Not provided</td>
<td>Optic neuropathy 13.0%</td>
<td>Cranial nerve III palsy (5/46, 53%)</td>
</tr>
<tr>
<td>Vaa Stavern et al.</td>
<td>2000</td>
<td>M = 203</td>
<td>326</td>
<td>Head trauma patients</td>
<td>2-86, 30</td>
<td>3 days-12 years, 73.5 days</td>
<td>MVA 165/266, 59.8%</td>
<td>Retrochiasmal VF defect</td>
<td>Cranial nerve IV palsy (4/266, 41.2%)</td>
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</tbody>
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<th>Author</th>
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<tr>
<td>Jacobs et al.</td>
<td>1989</td>
<td>M = 96</td>
<td>96</td>
<td>Motorcycledepressed accident victims with N.O. abnormalities</td>
<td>15-52, 25.5</td>
<td>Not provided</td>
<td>Motorcycle accident 949/6, 97.9%</td>
<td>Traumatic optic neuropathy 1649/6, 16.7%</td>
<td>Cranial nerve III palsy (13/6, 21.1%)</td>
</tr>
<tr>
<td>Sabatino et al.</td>
<td>1991</td>
<td>M = 125</td>
<td>181</td>
<td>Ps referred with visual complaints after head trauma</td>
<td>5-74, 31</td>
<td>3-63 yrs, 8.3</td>
<td>MVA 199/181, 57%</td>
<td>Functional visual field defect</td>
<td>Cranial nerve IV palsy (13/181, 7.2%)</td>
</tr>
<tr>
<td>Keane (8)</td>
<td>1998</td>
<td>M = 5</td>
<td>21/5, 42%</td>
<td>Head trauma patients referred from rehab</td>
<td>24/5, 48%</td>
<td>2/5, 40%</td>
<td>3/5, 60%</td>
<td>2/5, 40%</td>
<td>LOC and VF defect</td>
</tr>
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<td>2000</td>
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</tr>
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TABLE 4. Neuro-ophthalmic findings in head trauma—literature review

Abnl, abnormality; bilat, bilateral; LOC, loss of consciousness; M, men; MVA, motor vehicle accident; N.O., neuro-ophthalmic; Ps, patients; VF, visual field; W, women.
DISCUSSION

Head trauma is common. In one survey, the incidence of traumatic head injury requiring hospitalization ranged from 109 to 322 per 100,000 people (4). The advent of motorized transportation has increased the clinician's exposure to head trauma and its complications. Indeed, MVA is the most frequent cause of head injury in the United States. Young men are most frequently affected (4,5), as noted in our study (Table 4).

The relationship between head trauma and neuro-ophtalmic injury has been recognized for some time. Indeed, Hutchinson's studies (6) in the 1880s documented a clear relation between head trauma and ocular motility deficits. Surprisingly, there have been relatively few large studies assessing the frequency of specific neuro-ophtalmic deficits seen in association with head trauma (Table 4). The relative frequency of neuro-ophtalmic deficits is highly variable, and this finding may be explained by differences in the patient population. However, a few studies reviewed patient populations that were homogeneous in age or clinical characteristics; for example, Lepore (11) studied motility deficits in patients with known heterodivergences and subjective diplopia, thereby perhaps missing patients with only afferent, or afferent and efferent, deficits (Table 4). Furthermore, in some reviews, certain aspects of the neuro-ophtalmic examination (such as visual field defects) were not addressed. Finally, referral bias may play a role in that patients with only mild neuro-ophtalmic deficits or patients whose neurologic status renders them unable to communicate symptoms may not be referred to the neuro-ophtalmologist. It is very likely that we had such a bias, because not all patients with head trauma were evaluated by us; however, we think that our series is most likely representative of the population with severe head trauma. Indeed, almost all our patients were referred from the rehabilitation service, where they were admitted for at least 3 to 4 weeks. This neuro-ophtalmic evaluation was part of a routine evaluation performed before their discharge. Only 56.7% of our patients had an abnormal neuro-ophtalmic examination, suggesting that not only symptomatic patients were referred to us.

Closed head injury may damage the optic nerve through a variety of mechanisms, including direct injury from a penetrating wound, indirect injury from concussive forces transmitted to the nerve, and disc edema from elevated intracranial pressure (2). Indirect optic nerve injury is the most common form of traumatic optic neuropathy (TON) (2). The incidence of indirect TON ranges from 2.8 to 26.1% (Table 4). This large range is most likely related to several factors: 1) TON may be difficult to diagnose in the acutely ill, head-injured patient; 2) distinction between the mechanisms of TON (direct vs. indirect injury, papilledema) requires adequate historical information and accurate and reliable visual field testing, both of which may be difficult to obtain in neurologically impaired patients; and 3) attention is often directed to efferent pathway deficits because these are more amenable to management. Our study showed a higher incidence of indirect TON than many previous studies, suggesting that TON may be underdiagnosed in the head trauma population. Although the management of indirect TON is controversial, patients with indirect TON seen within the first few hours may benefit from treatment with high-dose corticosteroids (1,2,14,15). Therefore, indirect TON should always be suspected in patients with severe head trauma.

Traumatic chiasmal injury is uncommon and is often associated with frontal head trauma. Typical features include bitemporal hemianopia (often complete), cerebrospinal fluid rhinorrhea, and diabetes insipidus. The mechanism of injury is unclear but may involve physical disruption of the chiasm or diffuse axonal injury (1). Only three of our patients had chiasmal injury, attesting to the rarity of the phenomenon.

Because a relatively large proportion of neural tissue is dedicated to the primary retrochiasmal visual system, it makes intuitive sense that diffuse brain injuries should frequently damage these pathways; however, the relative frequency of traumatic retrochiasmal visual field defects is difficult to ascertain in the literature, because many studies do not specifically address this issue. This observation may again reflect the difficulty in assessing visual fields in neurologically impaired patients, particularly using the automated perimetry. We were able to obtain a reliable visual field test in all our patients, using the Humphrey automated perimeter or Goldmann visual field test performed by a skilled technician in patients with cognitive disorders. More than half of our patients with afferent pathway deficits had retrochiasmal visual field defects, a much higher incidence than that reported in comparable studies. Because these visual field defects may have substantial financial and legal implications (regarding driving and employment), accurate visual field testing is critical in head-injured patients. Because accurate testing is often not possible in the immediate period after the injury and may not be possible for weeks or even months after the injury, it is important that patients be monitored at regular intervals until an accurate assessment can be made.

The ocular motor nerves may be damaged at any point in their course from brainstem nucleus to extraocular muscle. The most likely mechanism of injury is axonal shearing resulting from differential acceleration of the skull and brain (2,3); however, focal lesions such as hemorrhage at the brainstem exit site (16) or avulsion of the nerve root (12) may also occur. In some cases, minor head trauma may unmask a pre-existing, otherwise unrecognized mass lesion (17).

The trochlear nerve is the smallest and longest of the ocular motor nerves and is closely associated with the rigid tentorium, making it susceptible to traumatic injury. It is particularly susceptible to injury as it emerges from the dorsal surface of the brainstem; damage at this location often causes bilateral injury (1). The fourth nerve has been variably reported to be the most and least frequently involved ocular motor nerve after head trauma.
pranuclear disorders, particularly convergence insufficiency, may be relatively asymptomatic and therefore not promptly recognized ocular motor nerve palsy in any age group. A high proportion (32.5%) was bilateral, reinforcing the concept that a bilateral trochlear nerve palsy should be suspected in any patient with what appears to be a unilateral injury. Further, a certain proportion of posttraumatic trochlear nerve injury may represent decomposition of a pre-existing congenital trochlear nerve palsy. Indeed, in one study, congenital trochlear nerve palsy was the most common cause in children (20). Determination of vertical fusion amplitude and examination of old photographs usually help to distinguish congenital from acquired trochlear nerve palsy.

Trauma is the second or third leading cause of ocular motor nerve palsies in adults and the leading cause of acquired third nerve palsies in children (1,20,21). The site of injury is often difficult to localize unless other neurologic findings are present. Among our patients with ocular motor nerve palsies, oculomotor nerve injury was the second most common deficit, found in 46.4% of patients with oculomotor nerve palsies; only 7.7% were bilateral.

Acquired abducens nerve palsy is the most commonly recognized ocular motor nerve palsy in any age group (1,19,21). This finding probably relates more to the ease of diagnosis rather than frequency of occurrence, because acquired abducens nerve palsies are relatively rare in certain age groups, such as young adults (22). The abducens nerve has a long course and is susceptible to injury at any point; it is particularly vulnerable to the effects of elevated intracranial pressure. The abducens nerve was the least commonly affected ocular motor nerve in the previous studies (Table 4), and this finding is in agreement with our series.

Convergence insufficiency is a supranuclear motility disorder characterized by a remote near point of convergence, poor convergence amplitudes, and an exodeviation at near. Convergence insufficiency may be seen in a variety of clinical settings, but its association with head trauma has been well documented (3). Similar to previous studies (Table 4), convergence insufficiency was the most common supranuclear ocular motility deficit among our patients, seen in 14.7% of patients with different deficits. Other supranuclear motility disorders (such as supranuclear gaze palsies, skew deviation, and dorsal midbrain syndrome) are less commonly reported in association with head trauma. This finding may again reflect difficulty in diagnosing these deficits in uncooperative patients. In addition, some of these disorders may be relatively asymptomatic and therefore not prompt referral to a neuro-ophthalmologist. Furthermore, these supranuclear disorders, particularly convergence insufficiency, may be masked by coexistent ocular motor deficits (11).

Knowing if specific neuro-ophthalmic deficits were more common after certain types of head injury might allow the clinician to have a higher index of suspicion for certain abnormalities when examining these patients. Loss of consciousness (LOC) implies head injury severe enough to cause brainstem reticular formation or bitemporal hematoma due to diffuse axonal injury, parenchymal contusion, or ICH. Several studies have found a correlation between LOC and particular neuro-ophthalmic deficits (9,23); however, LOC was not significantly associated with any outcome in our study. This finding would suggest that although LOC may be an indirect indicator of the severity of head injury, it may not be a reliable predictor of neuro-ophthalmic outcomes. The presence of a neuroimaging abnormality (skull fracture, contusion, or ICH) would suggest a greater severity of head trauma and perhaps a more frequent occurrence of certain neuro-ophthalmic deficits. In our study, the presence of an ICH was significantly, and strongly, correlated to unilateral oculomotor palsy. The presence of a skull fracture was significantly, but weakly, correlated to unilateral abducens nerve palsy. The specific location and extent of the neuroimaging abnormalities were not available in all patients; however, the information available would suggest that the presence of a neuroimaging abnormality, especially ICH, should increase the index of suspicion for an ocular motor nerve injury, particularly of the oculomotor nerve.

Finally, it is worth mentioning that more than one third (34.3%) of our patients with neuro-ophthalmic deficits had normal neuro-imaging. Therefore, even in the absence of any neuroimaging abnormality, the prevalence of neuro-ophthalmic findings is high.

REFERENCES


When Does Low Mean High? Isolated Cerebral Ventricular Increased Intracranial Pressure in a Patient With a Chiari I Malformation

Raymond R. Lancione, Jr., MD, and Gregory S. Kosmorsky, DO

Objective: To present an unusual case of pseudotumor cerebri with increased intracranial pressure isolated to the cerebral ventricles resulting from a Chiari I malformation.

Materials and Methods: The patient received a complete ophthalmologic examination on initial presentation and subsequent visits, including visual acuity, pupillary examination, intraocular pressures, dilated fundus examination with assessment of degree of papilledema, and visual field testing. Intracranial pressure was measured by lumbar puncture and subsequently by intracranial pressure bolt monitoring. Magnetic resonance imaging (MRI) was used to diagnose the Chiari I malformation.

Results: The patient initially presented with bitemporal headaches, elevated opening pressure on lumbar puncture, and mild papilledema with a normal MRI. After lumboperitoneal shunt placement and several revisions, the patient presented with decreased vision OD secondary to Terson syndrome and worsening papilledema. Subsequent evaluation revealed normal lumbar opening pressures and a Chiari I malformation. She underwent ventriculoperitoneal shunt placement with resolution of her symptoms.

Conclusions: Tonsillar herniation is a well-documented complication of lumboperitoneal shunt revision. Obstruction of cerebrospinal flow through the foramina of Magendie and Luschka can result in increased intracranial pressure isolated to the cerebral ventricles. In a patient with signs and symptoms of increased intracranial pressure but normal lumbar opening pressure, a Chiari I malformation should be suspected, particularly with a history of multiple lumboperitoneal shunt revisions.

Key Words: Pseudotumor cerebri—Increased intracranial pressure—Chiari malformation—Tonsillar herniation—Terson syndrome.

A 42-year-old woman presented initially in July 1994 with severe bitemporal headaches and was diagnosed with pseudotumor cerebri based on a normal magnetic

FIG. 1. Optic disc and fundus photos A: OD and B: OS, showing 4+ papilledema and subretinal hemorrhage consistent with Terson syndrome. Note subretinal hemorrhage involving the fovea OD.
WHEN DOES LOW MEAN HIGH?

followed by loss of central vision OD. She was evaluated the next day.

Vision was counting fingers at 15 feet OD and 20/20 OS. Near vision was 20/400 OD and J1 OS. Pupillary reactions were 2+ OU without a relative afferent pupillary defect. Extracocular muscle motility was full OU. Slit lamp examination of the anterior segment was within normal limits OU. Applanation tensions were 18 mm Hg OD and 17 mm Hg OS. Dilated fundus examination revealed 4+ papilledema and subretinal hemorrhage OU with involvement of the fovea OD, findings consistent with Terson syndrome and accounting for her loss of acuity and the lack of a relative afferent papillary defect (Fig. 1) (1,2).

On March 12, 1999, the patient underwent a fluoroscopic lumbar puncture, which yielded clear fluid and an opening pressure of 150 cm H2O. MRI of the brain showed a large Chiari I malformation with herniation of the cerebellar tonsils through the foramen magnum (Fig. 2). On March 29, 1999, the patient noticed a sudden decrease in visual acuity OS. Her vision was 20/400 OD and 20/200 OS. Dilated fundus examination revealed subretinal hemorrhage involving the fovea OS. The fundus OD also worsened, with the development of more extensive retinal edema (Fig. 3). Despite two normal lumbar opening pressures, an elevation of intracranial pressure was strongly suspected given her high-grade papilledema. Intraoperative intracranial pressure bolt monitoring was used to record a pressure of 340 cm H2O in the lateral ventricles, confirming increased intracranial pressure and noncommunication of the cerebral ventricular system with the lumbar thecal space, presumably at the level of the foramina of Magendie and Luschka. Subsequently, the patient underwent ventriculoperitoneal shunt placement with rapid resolution of her papilledema (Fig. 4). The extensive subretinal hemorrhage OU also regressed with treatment.

resonance imaging (MRI) scan and an opening pressure on lumbar puncture of 320 cm H2O, with a normal cerebrospinal fluid constituency. The patient had mild papilledema and no visual field loss at that time. Her headaches persisted, and in February 1995, the patient had her first lumboperitoneal shunt. From this time until November 30, 1998, she had seven shunt revisions. On February 10, 1999, the shunt was confirmed to be nonfunctional and was removed. Opening pressure by lumbar puncture was 140 cm H2O at that time, despite a nonfunctioning shunt. On March 1, 1999, the patient began having seizures. One week later, she had a seizure

FIG. 2. Magnetic resonance image of the brain showing tonsillar herniation through the foramen magnum.

FIG. 3. Fundus photos A: OD and B: OS, showing worsening Terson syndrome with bilateral foveal involvement of subretinal hemorrhage.
DISCUSSION

The Chiari I malformation is a well-documented complication of lumboperitoneal shunting, and in this case, the patient had several revisions of her shunt, which led to an acquired Chiari I malformation (3,4). Obstruction of the outflow of cerebrospinal fluid at the foramen magnum caused by tonsillar herniation led to an elevated intracranial pressure isolated to the cerebral ventricles. Although this event is rare, isolation of increased intracranial pressure to the ventricles must be considered when the signs and symptoms of increased intracranial pressure persist in the face of normal lumbar puncture opening pressures. This finding is more likely if the patient has undergone multiple lumboperitoneal shunts, a common cause of an acquired Chiari I malformation.

REFERENCES

Sleep Disorders: A Risk Factor for Pseudotumor Cerebri?

Dennis M. Marcus, MD, Julie Lynn, MD, John J. Miller, MD, Omar Chaudhary, Dilip Thomas, MD, and Bashir Chaudhary, MD

Objective: To determine whether sleep-related breathing disorders are common in patients with idiopathic intracranial hypertension.

Materials and Methods: Medical records of 53 patients with idiopathic intracranial hypertension from a tertiary center neuro-ophtalmology practice were reviewed. Thirty-seven patients were identified who had a history of snoring, difficulty sleeping, or daytime somnolence. The data from polysomnograms were tabulated to determine the frequency of apneas, hypopneas, and arousals.

Results: Fourteen of 37 patients with idiopathic intracranial hypertension and symptoms of sleep disturbance underwent polysomnography. There were two men and 12 women varying in age from 24 to 58 years (mean, 39.4 ± 11.9). These patients were obese with body mass indexes varying from 33.0 to 63.2 (mean, 46.0 ± 9.5). A diagnosis of sleep apnea was made in six and upper airway resistance syndrome in seven patients.

Conclusions: Sleep-related breathing problems were common in our patients with idiopathic intracranial hypertension. Obesity was common in these patients and may be playing a causative role in sleep apnea and idiopathic intracranial hypertension. It is suggested that idiopathic intracranial hypertension patients who have symptoms of sleep disturbance should be further evaluated for the presence of sleep-related breathing problems.

Key Words: Idiopathic intracranial hypertension—Pseudotumor cerebri—Papilledema—Sleep apnea—Sleep hypopnea—Upper airway resistance syndrome—Sleep disorders.

Idiopathic intracranial hypertension is characterized by optic disc edema, elevated intracranial pressure, normal spinal fluid constituents, and absence of evidence of a mass lesion on neuroimaging (1,2). Idiopathic intracranial hypertension occurs predominantly in young, middle-aged, obese women, and case-control studies confirm that obesity and recent weight gain are more common in patients with idiopathic intracranial hypertension than in controls (3–7). Decreased cerebrospinal fluid (CSF) absorption by arachnoid villi or elevated intracranial venous pressures are mechanisms often proposed as final common pathways of multiple inciting factors (8–10).

Sleep apnea is a common sleep-related breathing disorder characterized by daytime hypersomnolence, snoring, and multiple episodes of apnea (cessation of airflow) or hypopnea (reduction in airflow) during sleep (11). A mild form of the disease is called upper airway resistance syndrome (UARS) in which repeated arousals from sleep occur because of an increased effort to breathe to overcome the narrowing of the upper airways (12).

The ocular manifestations of sleep apnea have been described in case reports or small series, and optic disc edema (13–19), glaucomatous (20), and ischemic optic neuropathy (21) have been observed. Seven case reports note the association of optic disc edema with and without increased intracranial pressure in seven sleep apnea patients (13–19). Thus, sleep apnea has been proposed to be an uncommon but recognized cause of idiopathic intracranial hypertension (18). We determined the frequency of sleep-disturbed breathing and sleep disorders in our patient population with idiopathic intracranial hypertension.

METHODS

Our institution's human assurance committee approved the study protocol. We reviewed the records of patients with a diagnosis of idiopathic intracranial hypertension. To be diagnosed with idiopathic intracranial hypertension, patients were required to demonstrate bilateral disc edema, a normal neuroimaging study, and a lumbar puncture showing normal CSF contents and high pressure.

A sleep history was obtained in 53 idiopathic intracranial hypertension patients. Polysomnography was recommended in all patients with a positive sleep history for snoring or daytime somnolence. Polysomnography was performed at night and consisted of 8-hour recordings of electroencephalograms (EEG), oculograms, chin muscle and anterior tibialis muscle electromyograms, electrocardiograms, oronasal airflow, and oxygen...
hypothesis was made in 13 of the 14 idiopathic intracranial hypertension patients. Sleep apnea was diagnosed in seven patients and UARS in six patients. One patient had snoring, but the number of arousals was fewer than the minimum required for the diagnosis of UARS.

**DISCUSSION**

Sleep-related breathing problems vary in severity from sleep apnea with respiratory failure to UARS. Patients with UARS usually do not have significant hypoxemia or hypercapnia. It is estimated that 4% of men and 2% of women in the general population have sleep apnea (11). The incidence of UARS may be higher than that of sleep apnea. The risk factors for sleep apnea include snoring, obesity, upper airway abnormalities, and alcohol intake.

The clinical features and pathophysiologic manifestations of patients with idiopathic intracranial hypertension and sleep disorders significantly overlap. Sex and age differences are the main distinguishing features between these two disorders. Sleep apnea is more common in middle-aged men, whereas idiopathic intracranial hypertension is more common in young women. Obesity is a significant risk factor for idiopathic intracranial hypertension and sleep-related breathing disorders. The prevalence of idiopathic intracranial hypertension in obese female patients more than 20% above ideal body weight is 19.3 per 100,000 compared with 1 per 100,000 in the normal, nonobese population (4). In one study, the prevalence of sleep apnea in morbidly obese patients was 77% in men and 7% in women (22). It is likely that obesity may play a central role in sleep apnea and idiopathic intracranial hypertension. Weight reduction is associated with improvement of symptoms in patients both of these diseases (23,24).

How might sleep disorders contribute to the development of idiopathic intracranial hypertension? Several factors including hypoxia, hypercapnia, polycythemia, and increased venous pressure have been postulated as

### TABLE 1. Demographics of idiopathic intracranial hypertension patients who did/did not undergo polysomnography

<table>
<thead>
<tr>
<th>Group A: polysomnography performed</th>
<th>Group B: polysomnography not performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
</tr>
<tr>
<td>Age</td>
<td>39.36 (SD: 11.86)</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>12/2</td>
</tr>
<tr>
<td>BMI</td>
<td>46.0 (SD: 9.525)</td>
</tr>
<tr>
<td>Average</td>
<td>23</td>
</tr>
<tr>
<td>SD</td>
<td>39.65 (SD: 9.2)</td>
</tr>
<tr>
<td>P value</td>
<td>0.93</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.

Frequency of apnea (cessation of breathing), hypopnea (reduction in ventilation limit oxygen desaturation), and arousal (increase in EEG frequency of at least 3 seconds) was determined.

Sleep apnea was diagnosed if the frequency of apnea and hypopnea per hour of sleep (i.e., respiratory disturbance index) was five or greater. UARS was diagnosed if the number of arousals per hour of sleep (arousal index) was 20 or greater and the arousals were associated with crescendo snoring.

**RESULTS**

Thirty-seven of 53 (70%) idiopathic intracranial hypertension patients had a history of sleep disturbance. Fourteen of these 37 patients underwent polysomnography (group A) and the 23 patients who declined polysomnography (group B) are summarized in Table 1. Almost all patients in both groups were morbidly obese (body mass index, >40). The differences between the two groups were not significant (P > 0.05).

The results of polysomnography in 14 patients are summarized in Table 2. A diagnosis of sleep-related problems was made in 13 of the 14 idiopathic intracranial hypertension patients.
potential causes for fundus abnormalities described in sleep apnea. Hypercapnia or hypoxia, particularly during sleep, is common in patients with sleep apnea. Nocturnal hypercapnia may be responsible for increased intracranial pressure and secondary papilledema in these cases (25). Episodic elevations in intracranial pressure have been shown during apneic episodes (26). Patients with severe obstructive sleep apnea may demonstrate contiguously elevated intracranial pressure (19).

Our data indicate that sleep-related breathing problems are common in patients with idiopathic intracranial hypertension. The high prevalence of sleep-related breathing disorders in our study may be somewhat inflated; patients with sleep apnea may be more likely to agree to have polysomnography than patients without. Those patients who underwent polysomnography, however, did not have substantially different demographic features compared with those patients who did not undergo polysomnography.

Our study suggests that sleep disorders may be a risk factor for idiopathic intracranial hypertension. These findings, however, do not provide evidence for a causally-effect relationship. Prospective studies are needed to confirm this association of these diseases. It is interesting to note that the only two male patients with idiopathic intracranial hypertension in our population were diagnosed as having sleep apnea. As idiopathic intracranial hypertension is uncommon in men, our findings support speculation that this association may be even more sex significant. We suggest that patients with idiopathic intracranial hypertension should be asked about the presence of symptoms of sleep apnea such as of snoring, disturbed sleep, and daytime somnolence. The presence of these symptoms should be an indication for further evaluation by polysomnography.

Acknowledgments: The authors thank Richard Rubin, MD, for contributing patients to this study.

REFERENCES

The SKILL Card Test in Optic Neuritis: Experience of the Optic Neuritis Treatment Trial

Danielle T. Long, MSPH, Roy W. Beck, MD, PhD, Pamela S. Moke, MSPH, R. Clifford Blair, PhD, Kevin E. Kip, PhD, Robin L. Gal, MSPH, Barrett J. Katz, MD, MBA, and the Optic Neuritis Study Group

Objectives: To assess the value of the Smith-Kettlewell Institute Low Luminance (SKILL) Card test, designed to measure vision at reduced contrast and luminance, among patients with previous optic neuritis.

Materials and Methods: The SKILL Card test was administered to 295 patients participating in the Optic Neuritis Treatment Trial (ONTT) follow-up study, concurrent with measurement of visual acuity, visual field, contrast sensitivity, and color vision. Health-related quality of life (HRQL) was also assessed in a subset of patients using the National Eye Institute Visual Function Questionnaire and an ONTT-developed questionnaire.

Results: The SKILL Card difference score (high-contrast acuity score minus low-contrast acuity score) was only weakly associated with the other measures of vision function ($r_s$ absolute range, 0.05-0.31) and with the HRQL measures ($r_s$ absolute range, 0.02-0.15). In contrast, the light and dark component scores of the SKILL Card test had higher associations with the other vision measures ($r_s$ absolute range, 0.27-0.54) and with the HRQL measures ($r_s$ absolute range, 0.16-0.40).

Conclusions: The SKILL Card difference score is not a meaningful measure for patients with optic neuritis; however, the test appears to have clinical usefulness as a method to measure high-contrast and low-contrast acuity.

Key Words: SKILL Card—High-contrast visual acuity—Low-contrast visual acuity—Optic neuritis—Health-related quality of life.

Most cases of optic neuritis recover to normal or near normal visual acuity, with or without corticosteroid treatment (1,2). However, even when acuity returns to normal, patients often still report visual difficulties (3,4). Some patients with normal acuity and perceived visual deficits may have abnormal contrast sensitivity, color vision, or visual field, whereas in other patients, these too may be normal.

The Smith-Kettlewell Institute Low Luminance (SKILL) Card test was designed to rapidly measure vision at reduced contrast and luminance. It has been reported to be a sensitive measure of optic nerve dysfunction that can detect visual abnormality in symptomatic post-optic neuritis patients (5). The test consists of two letter charts, mounted back-to-back and designed for a test distance of 40 cm. One side is a high-contrast black-on-white letter chart with letter sizes from 20/12.5 to 20/630; the other side is a low-contrast (approximately 14%) chart comprised of black letters ranging in size from 20/20 to 20/630 on a dark gray background (approximately 10% of the reflectance of white paper) designed to simulate low-luminance conditions. The background reflectance of the dark side results in a luminance approximately 1 log unit less than that of the light side. A difference score is computed by subtracting the number of letters correct on the dark chart from the number correct on the light chart.

In a previous study of 15 post-optic neuritis patients (with visual acuity of 20/40 or better), the SKILL Card difference score was abnormal in 73% of affected eyes and in 50% of eyes that had recovered to 20/20 or better acuity. In addition, 40% of unaffected fellow eyes had abnormal difference scores (6,7). The difference scores did not correlate with high- or low-contrast visual acuity, contrast sensitivity, color vision, or short- and middle-wavelength-sensitive cone increment thresholds, suggesting to the study's authors that it may be measuring a unique aspect of visual function.

We had the opportunity to assess the value of the SKILL Card test in a much larger population by administering it to patients participating in the Optic Neuritis Treatment Trial (ONTT). We describe the distribution of SKILL Card test scores and evaluate the relationship between SKILL Card test results and standard clinical measures of vision function. In addition, to evaluate whether the SKILL Card measures an aspect of vision function not measured by other vision tests, we assessed...
the relationship between the SKILL Card results and two health-related quality-of-life (HRQL) measures.

METHODS

The protocol, baseline characteristics of patients, and ONTT treatment trial results have been reported in previous publications (8–12). Briefly, 457 patients between ages 18 and 46 years with acute unilateral optic neuritis and no indication of a causal systemic disease other than multiple sclerosis (MS) were enrolled at 15 clinical centers. The primary visual outcome from treatment was assessed after 6 months. Patients continued to be monitored yearly to assess visual and neurologic courses. The study protocol was approved by the institutional review board at each clinical center. Written informed consent was obtained from each patient.

From 1995 to 1997 (5–8 years from study entry), the SKILL Card test was included as part of the testing at the annual examination of 311 patients. Because interpretation of the SKILL Card difference score requires good high-contrast acuity, patients with a visual acuity worse than 20/50 in one or both eyes were excluded from the analysis, reducing the sample size to 295.

The HRQL analysis was conducted on a subset of this cohort, comprised of patients who had completed one or both of the HRQL measures. The National Eye Institute Visual Function Questionnaire (NEI-VFQ) (13) was completed by 176 of the 295 patients, and a visual function questionnaire developed specifically for the ONTT (ONTT questionnaire) (3) was completed by 89 of the 295 patients (55 of whom were among those who completed the NEI-VFQ and 34 of whom were not).

SKILL Card and other visual function tests

The SKILL Card test was administered according to the testing protocol provided to us by its developers. A difference score was then calculated by subtracting the dark side score from the light side score. Based on a previous study of 203 individuals whose ages were similar to those of patients in our study, and unpublished information from the authors of that study, the normal range was considered to be less than or equal to 28 letters for the difference score, greater than or equal to 56 letters (logMar value = 0.63) for the light score, and greater than or equal to 76 letters for the dark score (5). The logMar values for the light and dark scores were used in the analyses.

During the same examinations, the other vision tests, administered by standard protocols (14,15), included: 1) visual acuity with a retroilluminated Early Treatment Diabetic Retinopathy Study (ETDRS) chart (normal range: logMar value < 0.07 [better than 20/20]), 2) contrast sensitivity with the Pelli–Robson chart (normal range ≥ 15 [approximately 1.75 log units]), 3) color vision with the Farnsworth–Munsell 100-hue test (normal range: error score ≤ 110), and 4) visual field with the Humphrey Field Analyzer (normal range: mean deviation ≥ -3.00).

Health-related quality-of-life measures

From 1996 to 1997, the 51-item field test version of the NEI-VFQ was included as part of the testing at annual examinations. Written instructions preceded the self-administered test. Thirteen subscales, scored on a 0 to 100-point scale (with 100 indicating highest function), were generated to assess areas of vision-related quality of life. For the analysis, only six subscales directly related to vision were used: general vision, near vision activities, distance vision activities, driving, color vision, and peripheral vision. A subscale was considered missing when one or more of its component items was missing. The question "At the present time, would you say your eyesight (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, very poor, or are you completely blind?" was used to create a dichotomous variable: excellent/good versus others.

The ONTT questionnaire, originally used for a treatment group comparison after 6 months in the ONTT (3), was administered a second time after the fifth annual visit. The questionnaire consisted of 29 questions that rated particular aspects of visual function and daily visual activities on a scale of 1 (excellent) to 5 (very poor). For analysis, the number of questions was reduced to 24 by excluding five items that in an internal consistency analysis correlated less than 0.20 with the average score of all items. A continuous test score was created as the average score of the 24 remaining answered questions. When responses were missing for five or more applicable questions, the questionnaire was not scored (this event applied to one patient). A dichotomous variable was created to distinguish patients who responded with "poor" or "very poor" on at least one question from those who did not.

Statistical analyses

Paired t tests and McNemar tests were used to compare the mean score and the proportion abnormal, respectively, on the SKILL Card and other vision tests between eyes with and without previous optic neuritis among the 230 patients with previous unilateral optic neuritis. Using data from the full cohort of 295 patients, a chi-squared test for trend was performed to assess whether the proportion of eyes with abnormal SKILL Card scores varied monotonically according to the number of other abnormal vision tests. Because of the skewed distributions of the vision test results, Spearman rank correlation coefficients, r (16), were computed to assess the association of the SKILL Card difference scores with the other visual function measures, and the association of each of the visual function measures and the questionnaire scores. When both eyes of a patient were included in an analysis, the P value was adjusted according to the method of Guiderman and Barlow (17,18). To ensure conservative estimation, we corrected for the maximum intereye intraclass correlation across all of the vision measures (r = 0.52). For the HRQL analysis, univariable logistic regression models were fit to estimate the odds ratio of an abnormal questionnaire score (as previously defined) comparing patients whose best eyes were
TABLE 1. Distribution of SKILL Card and other vision measure scores in patients with previous unilateral optic neuritis: a comparison of eyes with and without previous optic neuritis

<table>
<thead>
<tr>
<th>Measure of vision function</th>
<th>Eyes with a history of optic neuritis</th>
<th>Eyes without a history of optic neuritis</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) [% abnormal]</td>
<td>Mean (SD) [% abnormal]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N = 230)</td>
<td>(N = 550)</td>
<td></td>
</tr>
<tr>
<td>SKILL Card difference score</td>
<td>28 (10) [29]</td>
<td>25 (7) [30]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SKILL Card light score</td>
<td>0.02 (0.16) [30]</td>
<td>-0.04 (0.14) [19]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SKILL Card dark score</td>
<td>0.57 (0.25) [33]</td>
<td>0.46 (0.18) [18]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>-0.07 (0.14) [24]</td>
<td>-0.12 (0.11) [13]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>14.2 (1.5) [48]</td>
<td>15.4 (0.66) [8]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Color vision</td>
<td>114.8 (131.1) [32]</td>
<td>107.1 (56.3) [16]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Visual field</td>
<td>-1.8 (3.2) [27]</td>
<td>-1.30 (3.3) [10]</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Missing observations: color vision (18), visual field (19). SKILL Card difference scores are reported in number of letters (normal range ≥ 28 letters). SKILL Card light scores are reported in logMar conversions (normal range ≤ 0.07 [≥ 77 letters]). SKILL Card dark scores are reported in logMar conversions (normal range ≤ 0.63 [≥ 57 letters]). Visual acuity measured with a retroluminated ETDRS chart (normal range: logMar value < 0.0 [better than 20/20]). Contrast sensitivity was measured with a Pelli-Robson chart (normal range: contrast sensitivity score = 110). Color vision was measured with the Farnsworth-Munsell 100-hue test (normal range: color vision error score ≤ 110). Visual field was measured with the Humphrey Field Analyzer (normal range: mean deviation ≥ -3.00).
* The first P value is from a comparison of the means by a paired t test, and the second P value is from a comparison of the percent abnormal in each group by McNemar test.
SD, standard deviation; SKILL, Smith-Kettlewell Institute Low Luminance.

RESULTS

The 295 patients had an average age of 39 (± 7) years at the time of evaluation; 79% were women and 88% were white. Before the SKILL Card testing, 230 of the 295 patients had experienced optic neuritis in one eye and 65 had experienced optic neuritis in both eyes. The 176 patients who completed the NEI-VFQ were similar in age, sex, and race to the 119 patients who did not complete the NEI-VFQ. The 89 patients who completed the ONTT questionnaire were comparable to the 206 who did not with respect to age and sex, but a higher proportion of patients was white (97% vs. 85%; P = 0.003). Compared with the 162 ONTT patients who were not included in the study, the 295 patients included were slightly older on entry into the ONTT (mean 32 ± 7 years vs. 31 ± 6 years, P = 0.03) and more likely to be white (88% vs. 79%, P = 0.009).

Distribution of SKILL Card and other vision measure scores in eyes with and without optic neuritis

Among the 230 patients with one affected and one unaffected eye, the SKILL Card difference scores ranged from 1 to 73 in the eyes with previous optic neuritis and from 5 to 46 in eyes without previous optic neuritis. The eyes with previous optic neuritis had a mean light score of 79 ± 8 (logMar: 0.02 ± 0.16), mean dark score of 51 ± 13 (logMar: 0.57 ± 0.25), and mean difference score of 28 ± 10, whereas eyes without previous optic neuritis had scores of 82 ± 7 (logMar: -0.04 ± 0.14), 57 ± 9 (logMar: 0.46 ± 0.18), and 25 ± 7, respectively (Table 1).

As with the three SKILL Card measures, scores on each other visual function test were statistically worse in the eyes with previous optic neuritis than in the eyes without previous optic neuritis (P = 0.02 or smaller for all comparisons). However, the degree of abnormality generally was slight (Table 1).

TABLE 2. Percentage of eyes with abnormal SKILL Card scores according to the number of abnormal other vision measures

<table>
<thead>
<tr>
<th>Number of other vision tests abnormal*</th>
<th>Number of eyes</th>
<th>Eyes with abnormal SKILL Card difference score N (%)</th>
<th>Eyes with abnormal SKILL Card light score N (%)</th>
<th>Eyes with abnormal SKILL Card dark score N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>25 (10)</td>
<td>43 (29)</td>
<td>23 (79)</td>
</tr>
<tr>
<td>0</td>
<td>263</td>
<td>76 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>146</td>
<td>55 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>26 (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>31 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>19 (66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value†</td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Forty eyes did not have complete data for all vision tests and were excluded from the analysis. SKILL Card normal ranges: difference score: ≤ 28 letters; light score: ≤ 77 letters (logMar value ≤ 0.07); dark score: ≤ 57 letters (logMar value ≤ 0.63).
* Visual acuity, contrast sensitivity, color vision, and visual field.
† Corrected P value for trend.
SKILL, Smith-Kettlewell Institute Low Luminance.
Relationship of SKILL Card scores with other vision measures

In an analysis including all eyes with complete data, abnormal SKILL Card difference, light, and dark scores were all positively related to the number of other abnormal vision tests (all corrected P values for trend < 0.001; Table 2). However, among the 263 eyes that were in the normal range on each of the other four vision measures, 76 (29%) had an abnormal difference score. These 76 eyes were no more likely to have experienced previous optic neuritis (47% vs. 47%, P = 1.00) or to be from patients with MS (47% vs. 38%, P = 0.17) than the 187 eyes with a normal difference score.

Correlation coefficients between the SKILL Card difference score and the other measures of vision function were modest, ranging from 0.05 to 0.31 (absolute values) (Table 3). Both the light and dark score components of the SKILL Card test had considerably higher correlation with the other vision measures (absolute range, 0.27–0.54) than did the difference score.

Relationship of SKILL Card and other vision measure scores with health-related quality-of-life measures

The SKILL Card difference score was weakly associated or not associated with the NEI-VFQ subscale scores. Higher correlations with the NEI-VFQ scores were observed for the SKILL Card light and dark scores and for all of the other vision measures (Table 4).

Of all vision tests, the SKILL Card difference score also was found to have the weakest association with the single question on the NEI-VFQ in which the patients provided an overall rating of their vision. This result was seen when, based on a patient’s best eye on a given day.

### Table 3. Spearman correlation of conventional vision test scores with SKILL Card test scores (N = 590)

<table>
<thead>
<tr>
<th>Measure of vision function</th>
<th>Correlation with light score (r_s)</th>
<th>Correlation with dark score (r_s)</th>
<th>Correlation with difference score (r_s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td>0.54*</td>
<td>0.43*</td>
<td>0.05</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>0.33*</td>
<td>0.47*</td>
<td>0.33*</td>
</tr>
<tr>
<td>Color vision</td>
<td>0.36*</td>
<td>0.36*</td>
<td>0.19*</td>
</tr>
<tr>
<td>Visual field</td>
<td>0.27*</td>
<td>0.32*</td>
<td>0.16†</td>
</tr>
</tbody>
</table>

Missing observations: color vision (18), visual field (23). Visual acuity was measured with a retroilluminated ETDRS chart. Contrast sensitivity was measured with a Pelli-Robson chart. Visual field was measured with the Humphrey Field Analyzer. Color vision was measured with the Farnsworth-Munsell 100-hue test. In order to avoid potential interpretative difficulties, the signs of the correlation coefficients have been adjusted where necessary so that all visual measures are scaled in such manner as to associate higher scale values with better visual performance and lower values with worse visual performance.

* Corrected P value < 0.001.
† Corrected P value = 0.002.

### Table 4. Spearman correlation of the National Eye Institute Visual Function Questionnaire (NEI-VFQ) subscale scores with visual measures in best eye and worst eye of each patient (N = 176)*

<table>
<thead>
<tr>
<th>NEI-VFQ subscales</th>
<th>General vision (r_s)</th>
<th>Near activities (r_s)</th>
<th>Distance activities (r_s)</th>
<th>Driving (r_s)</th>
<th>Color vision (r_s)</th>
<th>Peripheral vision (r_s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKILL Card difference score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best eye</td>
<td>0.02</td>
<td>0.07</td>
<td>0.05</td>
<td>-0.05</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.04</td>
<td>0.15</td>
<td>0.08</td>
<td>-0.02</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>SKILL Card light score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best eye</td>
<td>0.31†</td>
<td>0.30†</td>
<td>0.20†</td>
<td>0.18†</td>
<td>0.25†</td>
<td>0.10</td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.40†</td>
<td>0.36†</td>
<td>0.28†</td>
<td>0.22†</td>
<td>0.23†</td>
<td>0.21†</td>
</tr>
<tr>
<td>SKILL Card dark score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best eye</td>
<td>0.24†</td>
<td>0.32†</td>
<td>0.20†</td>
<td>0.21†</td>
<td>0.16†</td>
<td>0.17†</td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.32†</td>
<td>0.36†</td>
<td>0.26†</td>
<td>0.23†</td>
<td>0.18†</td>
<td>0.25†</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>0.25†</td>
<td>0.28†</td>
<td>0.16†</td>
<td>0.16†</td>
<td>0.18†</td>
<td>0.11</td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.34†</td>
<td>0.30†</td>
<td>0.27†</td>
<td>0.23†</td>
<td>0.18†</td>
<td>0.21†</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best eye</td>
<td>0.23†</td>
<td>0.21†</td>
<td>0.25†</td>
<td>0.19†</td>
<td>0.19†</td>
<td>0.19†</td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.30†</td>
<td>0.26†</td>
<td>0.27†</td>
<td>0.17†</td>
<td>0.14</td>
<td>0.33†</td>
</tr>
<tr>
<td>Color vision</td>
<td>0.19†</td>
<td>0.21†</td>
<td>0.17†</td>
<td>0.07</td>
<td>0.19†</td>
<td>0.34†</td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.24†</td>
<td>0.20†</td>
<td>0.24†</td>
<td>0.10</td>
<td>0.16†</td>
<td>0.35†</td>
</tr>
<tr>
<td>Visual field</td>
<td>0.24†</td>
<td>0.11</td>
<td>0.18†</td>
<td>0.12</td>
<td>0.22†</td>
<td>0.24†</td>
</tr>
<tr>
<td>Worst eye</td>
<td>0.29†</td>
<td>0.15</td>
<td>0.22†</td>
<td>0.15</td>
<td>0.19†</td>
<td>0.38†</td>
</tr>
</tbody>
</table>

In order to avoid potential interpretative difficulties, the signs of the correlation coefficients have been adjusted where necessary so that all visual measures are scaled in such manner as to associate higher scale values with better visual performance and lower values with worse visual performance. * The effective n varies from 150 to 173 across correlations of vision tests and subscales. † P value < 0.05.
## TABLE 5. Odds ratios for reported dysfunction on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) comparing the best 75% to the worst 25% of the distribution for the patients' better eyes on each visual function test

<table>
<thead>
<tr>
<th>Vision measure/eye</th>
<th>N</th>
<th>NEI-VFQ dysfunction*</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKILL Card difference score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>133</td>
<td>17 (13)</td>
<td>1.00</td>
<td>(0.41–3.01)</td>
<td>0.84</td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>43</td>
<td>6 (14)</td>
<td>1.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKILL Card light score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>133</td>
<td>9 (7)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>43</td>
<td>14 (33)</td>
<td>6.65</td>
<td>(2.63–16.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SKILL Card dark score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>133</td>
<td>11 (8)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>43</td>
<td>12 (28)</td>
<td>4.29</td>
<td>(1.73–10.65)</td>
<td>0.002</td>
</tr>
<tr>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>137</td>
<td>14 (10)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>39</td>
<td>9 (23)</td>
<td>2.64</td>
<td>(1.04–6.66)</td>
<td>0.04</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>153</td>
<td>14 (9)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>23</td>
<td>9 (39)</td>
<td>6.38</td>
<td>(2.34–17.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Color vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>128</td>
<td>11 (9)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>42</td>
<td>11 (26)</td>
<td>3.77</td>
<td>(1.50–9.52)</td>
<td>0.005</td>
</tr>
<tr>
<td>Visual field</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>127</td>
<td>15 (12)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>42</td>
<td>7 (17)</td>
<td>1.49</td>
<td>(0.56–3.96)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Missing observations: color vision (6), visual field (7).

* NEI-VFQ dysfunction defined as a response of fair, poor, very poor, or completely blind on the question, "At the present time, would you say your eyesight (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, very poor, or are you completely blind?"

For each vision measure, the patients in the worst quartile of scores were compared with patients in the remaining 75% of the distribution (Table 5). Unlike the SKILL Card difference score, the light and dark component scores were strongly associated with the responses on this global NEI-VFQ question. Results were similar for each vision test when patients with a normal score in both eyes were compared with those with an abnormal score in at least one eye. Each of the other four vision measures, and the light and dark SKILL scores, showed a strong association with the

## TABLE 6. Odds ratios for reported dysfunction on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) comparing normal and abnormal patients on each visual function test (N = 176)

<table>
<thead>
<tr>
<th>Vision measure*</th>
<th>N</th>
<th>NEI-VFQ dysfunction†</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKILL Card difference score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>76</td>
<td>8 (11)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>100</td>
<td>15 (15)</td>
<td>1.50</td>
<td>(0.60—3.75)</td>
<td>0.39</td>
</tr>
<tr>
<td>Light side SKILL score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>108</td>
<td>4 (4)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>68</td>
<td>19 (28)</td>
<td>10.08</td>
<td>(3.26—31.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dark side SKILL score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>105</td>
<td>7 (7)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>71</td>
<td>16 (23)</td>
<td>4.07</td>
<td>(1.58—10.51)</td>
<td>0.004</td>
</tr>
<tr>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>122</td>
<td>10 (8)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>54</td>
<td>13 (24)</td>
<td>3.55</td>
<td>(1.45—8.72)</td>
<td>0.006</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>93</td>
<td>4 (5)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>93</td>
<td>19 (20)</td>
<td>5.07</td>
<td>(1.65—15.60)</td>
<td>0.005</td>
</tr>
<tr>
<td>Color vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>113</td>
<td>7 (6)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>57</td>
<td>15 (26)</td>
<td>5.41</td>
<td>(2.06—14.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visual field</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>119</td>
<td>11 (9)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>50</td>
<td>11 (22)</td>
<td>2.77</td>
<td>(1.11—6.90)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Missing observations: color vision (6), visual field (7).

* For vision measures, patients were considered normal when the test score was in the normal range in both eyes and abnormal when the test score in at least one eye was abnormal.

† NEI-VFQ dysfunction defined as a response of fair, poor, very poor, or completely blind on the question, "At the present time, would you say your eyesight (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, very poor, or are you completely blind?"
TABLE 7. Spearman correlation of visual measures in best and worst eye with Optic Neuritis Treatment Trial (ONTT) questionnaire score

<table>
<thead>
<tr>
<th>Measure of vision function</th>
<th>Best eye ($r_s$)</th>
<th>Worst eye ($r_s$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKILL Card difference score</td>
<td>0.13</td>
<td>0.04</td>
</tr>
<tr>
<td>SKILL Card light score</td>
<td>0.28*</td>
<td>0.33*</td>
</tr>
<tr>
<td>SKILL Card dark score</td>
<td>0.28*</td>
<td>0.33*</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>0.16</td>
<td>0.23*</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>0.20</td>
<td>0.35*</td>
</tr>
<tr>
<td>Color vision</td>
<td>0.36*</td>
<td>0.38*</td>
</tr>
<tr>
<td>Visual field</td>
<td>0.21*</td>
<td>0.28*</td>
</tr>
</tbody>
</table>

Missing observations: color vision (1). Visual acuity was measured with a retroilluminated ETDRS chart. Contrast sensitivity was measured with a Pelli-Robson chart. Visual field was measured with the Humphrey Field Analyzer. Color vision was measured with the Farnsworth-Munsell 100-hue test. In order to avoid potential interpretative difficulties, the signs of the correlation coefficients have been adjusted where necessary so that all visual measures are scaled in such a manner as to associate higher scale values with better visual performance and lower values with worse visual performance.

* $P$ value < 0.05.

NEI-VFQ global vision question, whereas the SKILL Card difference score did not (Table 6). Replicating the analyses using the ONTT questionnaire rather than the NEI-VFQ, the results were very similar, particularly when the smaller sample size was considered (Table 7 and Table 8).

DISCUSSION

The SKILL Card was developed to provide a measure of visual function at low contrast and reduced luminance to simulate a condition in which people often describe visual difficulties in day-to-day living (5). This development has particular potential relevance for patients with optic nerve disease who often have visual complaints even when visual acuity is normal or near normal (3).

In this study, we found the SKILL Card difference score to be somewhat discriminating between eyes with and without previous optic neuritis in that eyes that had previous optic neuritis had worse scores on average than eyes that did not, although the magnitude of the difference (approximately three letters) is not likely to be clinically relevant. The percentage of eyes with abnormal SKILL Card difference scores was higher than the abnormal percentage for each of the other measures, and even when all other vision measures were in the normal range, the SKILL Card difference score was abnormal in more than one quarter of the eyes. The SKILL Card difference score was poorly correlated with the other vision measures, whereas the individual light and dark component scores had higher correlation.

Although our findings are consistent with the SKILL Card developers' contention that the difference score is a uniquely sensitive measure of subtle optic nerve dysfunction, the findings are also consistent with the possibility that the SKILL Card difference score has a high false-positive rate. We feel the latter is the more probable explanation. In support of this view is our finding that among eyes in which visual acuity, contrast sensitivity, color vision, and visual field were all normal, the eyes with an abnormal difference score were no more likely to have experienced previous optic neuritis or to be from patients with MS than the eyes with a normal difference score. Also, among all five vision tests, the SKILL Card difference score had the weakest association with the patient's self-reported visual impairment on the NEI-VFQ and the ONTT questionnaire. Because such HRQOL measures could reasonably be expected to detect the kind

TABLE 8. Odds ratios for reported dysfunction on the Optic Neuritis Treatment Trial (ONTT) questionnaire comparing the best 75% to the worst 25% of the distribution for the patients' better eyes on each visual function test

<table>
<thead>
<tr>
<th>Vision measure/eye</th>
<th>N</th>
<th>Abnormal on questionnaire* N (%)</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKILL Card difference score</td>
<td>68</td>
<td>34 (50)</td>
<td>1.00</td>
<td>(1.22-10.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>21</td>
<td>11 (52)</td>
<td>1.10</td>
<td>(0.41-2.93)</td>
<td>0.85</td>
</tr>
<tr>
<td>SKILL Card light score</td>
<td>69</td>
<td>32 (46)</td>
<td>1.00</td>
<td>(0.76-6.04)</td>
<td>0.15</td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>20</td>
<td>13 (65)</td>
<td>2.15</td>
<td>(1.14-10.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>70</td>
<td>31 (44)</td>
<td>1.00</td>
<td>(0.53-3.79)</td>
<td>0.49</td>
</tr>
<tr>
<td>SKILL Card dark score</td>
<td>19</td>
<td>14 (74)</td>
<td>3.52</td>
<td>(1.14-10.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>68</td>
<td>33 (49)</td>
<td>1.00</td>
<td>(0.60-6.37)</td>
<td>0.27</td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>21</td>
<td>12 (57)</td>
<td>1.41</td>
<td>(1.26-10.42)</td>
<td>0.02</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>75</td>
<td>36 (48)</td>
<td>1.00</td>
<td>(1.14-10.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>14</td>
<td>9 (64)</td>
<td>1.95</td>
<td>(1.26-10.42)</td>
<td>0.02</td>
</tr>
<tr>
<td>Best 75% of distribution</td>
<td>66</td>
<td>28 (42)</td>
<td>1.00</td>
<td>(1.22-10.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>22</td>
<td>16 (73)</td>
<td>3.49</td>
<td>(0.41-2.93)</td>
<td>0.85</td>
</tr>
<tr>
<td>Color vision</td>
<td>67</td>
<td>29 (43)</td>
<td>1.00</td>
<td>(0.41-2.93)</td>
<td>0.85</td>
</tr>
<tr>
<td>Worst 25% of distribution</td>
<td>22</td>
<td>16 (73)</td>
<td>3.49</td>
<td>(0.41-2.93)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

* The questionnaire was considered to be abnormal if the response to one or more questions was recorded as poor or very poor.
of real-world visual deficits that the SKILL Card was designed to measure, their lack of association with the SKILL Card difference score lends further support to the idea that the test has a high false-positive rate. Although we cannot completely rule out the possibility that the difference score is still measuring an aspect of visual function important to a patient with optic neuritis that is not being assessed in the questionnaires, this explanation seems unlikely, particularly in view of the consistency of the results using the two questionnaires. In addition, the fact that both the light and dark scores, from which the difference score is derived, correlated well with the other measures and with the questionnaires provides evidence that the test was administered properly.

Thus, in this study, we did not find evidence that the SKILL Card difference score is likely to benefit the clinician in assessing optic nerve dysfunction in patients after optic neuritis. It is probable that this result would be true for other optic neuropathies as well. Despite the lack of apparent value of the SKILL Card difference score, the component high-contrast (light) and low-contrast (dark) scores did appear to relate to a patient’s self-reported visual impairment as strongly as did the standard vision measures. Therefore, although the test may not be useful for its primary intended purpose, it may prove to be a useful test to obtain a rapid and easily administered assessment of high-contrast and low-contrast acuity.

Acknowledgments: The authors thank Marilyn Schneck, PhD, who provided review of the manuscript. The following are all principal investigators involved in the ONTT study since its onset in 1988 and all other investigators and clinical center staff active in the study since 1992.

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REFERENCES


Case Report

Neuro-Ophthalmic Manifestations of Sarcoidosis: Clinical Spectrum, Evaluation, and Management

Larry P. Frohman, MD, Ruben Grigorian, MD, and Leonard Bielory, MD

Objective: To familiarize the reader with the neuro-ophthalmic manifestations of sarcoidosis.

Materials and Methods: All patients underwent systemic evaluations (chest radiograph, magnetic resonance imaging and/or computed tomography, serum angiotensin-converting enzyme level, and gallium scan). Histologic confirmation was preferred (11 of 15 patients underwent biopsy, ten of whom [82%] had positive biopsies, and four refused). Otherwise, the diagnosis of clinical sarcoidosis was based on laboratory evaluation.

Results: We report our experience with 15 patients who had neuro-ophthalmic manifestations of sarcoidosis other than optic neuropathy or chiasmal disease. Eight of 15 (53%) did not have known sarcoidosis at the time of presentation. Thirteen of 15 (87%) patients demonstrated lesions consistent with sarcoidosis on magnetic resonance imaging of the brain. Treatment with corticosteroids and/or other immunomodulatory agents was necessary in all cases.

Conclusions: Neuro-ophthalmic manifestations of sarcoidosis are rare. They may be the presenting signs of otherwise occult disease. Suspicion and inclusion in the differential are a key to establishing the diagnosis. A strategy for the detection and evaluation of these cases is presented.

Key Words: Sarcoidosis—Diagnosis—Neuro-ophthalmic manifestations—Magnetic resonance imaging—Gallium scan.

Sarcoidosis is a worldwide disease affecting all ethnic groups with an overall incidence of 6 to 10 per 100,000 (1). There appears to be a racial predilection for the development of the disease with a prevalence of sarcoidosis in the United States of 5 in 100,000 in whites and 40 in 100,000 in blacks (2,3). Women seem to be more commonly affected than men (2). The peak incidence is in the young adult population (1). The ophthalmic manifestations of sarcoidosis are reported to occur in 22% of patients sometime in its course (4). Neurologic involvement has usually been reported to occur in approximately 5 to 16% of patients with sarcoidosis (5). When it occurs, central nervous system (CNS) involvement may be an early manifestation of the disease, unmasking otherwise undetected systemic sarcoidosis (6). Various neurologic manifestations have been observed, including seizures, cognitive or psychic manifestations, hypothalamic and pituitary involvement, focal pseudotumors, and hydrocephalus (often associated with lymphocytic meningitis). Furthermore, cranial nerve palsies, particularly palsy of the facial nerve, are not uncommon. Inclusion of facial nerve palsies that are peripheral (e.g., secondary owing to sarcoidosis of the parotid gland, the so-called Heerfordt disease) may make the incidence of primary neurologic sarcoidosis in reported series seem misleadingly high.

Neuro-ophthalmic involvement is rare but often severe. Patients with neuro-ophthalmic sarcoidosis, unlike those with nonspecific neurologic signs such as headache or irritability, may present early in its course, as the symptoms of diplopia and visual loss are typically immediately noted by the patient and reported to their physician. When the neuro-ophthalmic symptom is isolated, it may be difficult to diagnose the underlying disease.

SUBJECTS AND METHODS

A retrospective review of all patients seen on the Neuro-Ophthalmology Service from 1989 to 1999 revealed 15 patients (11 women [73%] and four men), with an age range of 27 to 76 years, who presented with neuro-ophthalmic findings other than disease of the optic nerve, chiasm, and optic tract, which ultimately was diagnosed as owing to sarcoidosis. As experience evolved during the decade, the evaluation of suspected neuro-ophthalmic sarcoidosis became more standardized.
**TABLE 1. Clinical presentation**

<table>
<thead>
<tr>
<th>Neuro-ophthalmic manifestations</th>
<th>1/6/2/6</th>
<th>1/7/2/6</th>
<th>6/2/2/6</th>
<th>4/6/2/6</th>
<th>5/7/2/6</th>
<th>6/2/2/6</th>
<th>7/3/2/6</th>
<th>8/2/2/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>6th nerve palsy</td>
<td>6th nerve palsy, nystagmus</td>
<td>6th nerve palsy, nystagmus</td>
<td>6th nerve palsy, proptosis</td>
<td>6th nerve palsy, proptosis, ON</td>
<td>6th nerve palsy, ON</td>
<td>6th nerve palsy, ON</td>
<td>6th nerve palsy, ON</td>
<td>6th nerve palsy, ON</td>
</tr>
<tr>
<td>Pain</td>
<td>+, headache</td>
<td>+, headache</td>
<td>+, headache</td>
<td>+, ocular</td>
<td>+, headache</td>
<td>+, headache</td>
<td>+, headache</td>
<td>+, headache</td>
</tr>
<tr>
<td>Preexisting sarcoid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ocular sarcoid</td>
<td>-</td>
<td>+ AU</td>
<td>OM + EL, CI</td>
<td>+, lacrimal gland</td>
<td>+, OM</td>
<td>+ EL</td>
<td>+, S, AU, V</td>
<td>+ K</td>
</tr>
<tr>
<td>Biopsy proven</td>
<td>+, lymph node</td>
<td>+, lung</td>
<td>+, lacrimal gland</td>
<td>+, conjunctiva</td>
<td>+, skin</td>
<td>+, lacrimal gland</td>
<td>+, conjunctiva</td>
<td>+, kidneys</td>
</tr>
</tbody>
</table>

* Not performed.
† Diplopia was treated 18 months before neuro-ophthalmologic assessment was performed and not characterized.
‡ Diplopia was not characterized.
§ Patient was sent for neuro-ophthalmology consult and cranial nerve involvement was not isolated; we included her in the study.

In most cases, the following laboratory evaluations were performed at presentation: chest radiograph (CXR), magnetic resonance imaging (MRI) of the brain (with fat-suppressed views of the optic nerves, with and without contrast), anergy panel, purified protein derivative (PPD), serum angiotensin-converting enzyme (ACE) level, 24-hour urine calcium, pulmonary function testing (PFT), lumbar puncture (LP), and gallium scan. Biopsy was performed in the 11 patients who permitted it.

**CLINICAL PRESENTATION**

Eleven women and four men with a mean age of 39.6 years (range, 27–76) were included in the study (Tables 1 and 2). Eight of 15 (53%) patients did not have known sarcoidosis at the time of neuro-ophthalmologic presentation. Six of 15 (40%) patients had an abducens nerve palsy: three had isolated involvement; one had a combined lesion with a facial nerve palsy; one had combined oculomotor, trochlear, trigeminal, and abducens nerve palsy; and one had pseudo Tolosa–Hunt syndrome. Three of 15 (20%) patients had an oculomotor nerve palsy: one had an isolated pupil-sparing third nerve palsy, one is a patient described previously, and one patient had combined pupillary oculomotor, trigeminal, and facial nerve palsies. Five of 15 (33%) patients had a facial nerve palsy: one had an isolated involvement, two patients with a combined involvement were described previously, one patient had it combined with fifth nerve palsy, and one had it combined with eighth nerve palsy. One patient had Parinaud syndrome. Two (13%) patients had unspecified diplopia. One (6.7%) patient had pericentral homonymous field defect with involvement of the occipital lobe.

Fourteen (93%) of the patients had pain (headache, n = 10 [71%]; ocular pain, n = 4 [29%]) at the time of neuro-ophthalmologic presentation. Eleven (73%) patients also had intraocular or orbital manifestations of sarcoidosis: five of these had anterior uveitis; one patient had scleritis, and one had vitreitis. Two (13%) patients had it combined with eighth nerve palsy. One patient had Parinaud syndrome. Two (13%) patients had unspecified diplopia. One (6.7%) patient had paracentral homonymous field defect with involvement of the occipital lobe.

**TABLE 2. Neurologic/ophthalmic manifestations of sarcoidosis (excluded optic neuropathy)**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial neuropathy</td>
<td></td>
</tr>
<tr>
<td>3rd (oculomotor)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Isolated</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Multiple</td>
<td>2 (13)</td>
</tr>
<tr>
<td>4th (trochlear)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>6th (abducens)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Isolated</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Multiple</td>
<td>3 (20)</td>
</tr>
<tr>
<td>7th (facial)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Isolated</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Multiple</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Parinaud syndrome</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Unspecified diplopia</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Paracentral homonymous field defect</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

* Refers to all patients (15) in the study.
an orbital mass, and one also had an enlarged lacrimal gland and conjunctivitis. Three (20%) patients had enlarged lacrimal gland with proptosis, one (7%) patient had pupillary synchia, and one (7%) patient had Koepppe nodules.

ILLUSTRATIVE CASE: PATIENT 1

A 30-year-old black woman was admitted to Neurology Service with a dull headache, bilateral blurred vision, and binocular diplopia that increased on right gaze, which progressed in severity over 1 week. Her medical history was significant for classic migraine. At presentation, her best visual acuity was 20/30 OU, examination revealed moderate abduction deficit OD, consistent with abducens paresis. The rest of her neurologic and ophthalmic examinations was normal. She was about to be discharged after a negative contrasted computed tomography (CT) scan of the head, with a working diagnosis of a first episode of ophthalmoplegic migraine; however, neuro-ophthalmic consultation believed that diagnosis to be unlikely. Because her pain was noted to be distributed in the first and second branches of the trigeminal nerve, a MRI scan of the brain, with contrast for attention to the cavernous sinus, was performed and demonstrated enhancement of the right cavernous sinus with a dural tail (Fig. 1).

Because of the suspicion of sarcoidosis, the patient’s evaluation included a normal serum ACE level and LP, a positive PPD (the patient later remembered that she had received Bacille Calmette-Guérin), and a normal CXR. Gallium scan revealed enhancement in the right axilla (Fig. 2) and led to axillary node biopsy, which revealed diffuse nonnecrotizing and necrotizing granulomas consistent with sarcoidosis. The patient was placed on 60 mg of oral prednisone daily, and her symptoms rapidly resolved.

Comment

The combination of a sixth nerve palsy and the trigeminal distribution of her pain localized the process to the cavernous sinus; thus, directed neuroimaging was performed. Sarcoidosis is in the differential of painful cavernous sinus masses with a dural tail (in the pre-MRI days, many such cases were labeled as Tolosa-Hunt syndrome). Gallium scan was used to indicate where to perform a tissue biopsy to obtain a histologic diagnosis.

LABORATORY EVALUATION

A CXR was performed on all patients: 10 (67%) patients had lesions on CXR consistent with sarcoidosis, six of which were histologically confirmed (Table 3). Of the five patients with a negative CXR, three permitted biopsy, and all had lesions consistent with sarcoidosis. Note that these three all had abnormal gallium scans, two of which had pulmonary uptake. The gallium scan was positive in 10 (71%) of the 14 patients tested.
Magnetic resonance imaging revealed lesions consistent with sarcoidosis in 13 (87%) cases, eight of which were confirmed by biopsy. The most common picture that we saw on the MRI scan was dural thickening with involvement of the cavernous sinus. In the three patients with a negative MRI, two had biopsy confirmation of sarcoidosis. Only three of 14 (21%) patients tested showed anergy. The serum ACE level was elevated in only four (27%) of 15 cases. Although serum ACE level is often said to be a marker for pulmonary activity, note that of the 11 patients in whom the ACE was negative, nine had an abnormal CXR, four of whom also had pulmonary uptake on gallium scan. PFTs were negative in all cases. The spinal fluid was abnormal in 2 of the 12 patients who had a LP (both revealed pleocytosis). Biopsies were consistent with sarcoidosis in 9 (82%) of 11 cases. Seven patients (47%) had biopsy-proven preexisting sarcoidosis. Sarcoid was suggested in patient 1 by a MRI scan, an abnormal gallium scan, and anergy (illustrative case). In patient 3, sarcoidosis was suggested by consistent MRI and gallium scan, an elevated ACE level, and orbital and lacrimal masses, with the latter yielding a positive biopsy.

### TREATMENT COURSE

The initial therapy of neurosarcoidosis is systemic corticosteroids (Table 4). All our patients received oral prednisone (initial dose, 1–1.5 mg/kg daily). The dose was tapered when the symptoms resolved (or in one case, withdrawn when there was no improvement). One patient developed adverse effects at levels of corticosteroids required to control his disease process. These were intolerable weight gain and steroid-induced diabetes and necessitated the addition of cyclosporine as a steroid-sparing agent. One patient did not respond to prednisone therapy and was changed to cyclosporine.

### DISCUSSION

Sarcoidosis is a systemic disease of unknown cause that commonly involves the eye and infrequently involves the CNS. The etiology of sarcoidosis is unknown. Evidence suggests that sarcoidosis occurs as the result of an imbalance in T-cell location and function, causing an exaggerated cellular immune response and an increased T-helper/inducer response (1).

There are several candidates for the inciting antigen; recent evidence points to infectious agents, especially...
### TABLE 4. Treatment course

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Corticosteroids</th>
<th>Cyclosporine</th>
<th>Comment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td></td>
<td>Started on cyclosporine owing to inability to tolerate corticosteroids</td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia in end gaze</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td></td>
<td>Cyclosporine started because of inability to stabilize symptoms with corticosteroids</td>
<td>Symptom free, residual diplopia in end gaze</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>13</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>14</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td></td>
<td></td>
<td>Symptom free, residual diplopia corrected with the prism</td>
</tr>
</tbody>
</table>

*Lower et al.* (8) identified patients with neurologic manifestations of sarcoidosis. At their institution, 71 (13%) of 554 patients with sarcoidosis (definite or probable status) had evidence of nervous system involvement. Seventy (94%) patients with sarcoidosis (definite or probable status) had evidence of nervous system involvement. Seventy (94%) patients with sarcoidosis (definite or probable status) had evidence of nervous system involvement. Seventy (94%) patients with sarcoidosis (definite or probable status) had evidence of nervous system involvement. Seventy (94%) patients with sarcoidosis (definite or probable status) had evidence of nervous system involvement.

Neuro-ophthalmic manifestations of sarcoidosis are rare and include optic neuritis, paracentral field defect (involvement of the optic nerve on MRI) and one with Parinaud syndrome (Table 1). MRI revealed lesions consistent with sarcoidosis in 13 (87%) patients (Table 3). Five (33%) patients had evidence of seventh nerve involvement, four of whom had characteristic changes for sarcoidosis on MRI.

Physicians need be aware that sarcoidosis can present initially with a neurologic-ophthalmic manifestation. MRI of the brain or orbits is the best choice for initial imaging study. If sarcoidosis is suggested by the MRI findings, which may include lacrimal gland, meningeal

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*Mycobacterium* species (5). Sarcoid granulomas are typically noncaseating and consist of epithelioid cells that are surrounded by a border of mononuclear cells, usually lymphocytes (7). Organ dysfunction seems to result from distortion of the normal architecture of the affected tissue by granulomas and subsequent fibrosis rather than by production of mediators that lead to damage (1). Neurologic sarcoidosis represents an uncommon but serious manifestation of sarcoidosis (8). When neurologic involvement occurs in the course of known sarcoidosis, the diagnosis of neurosarcoidosis is typically suspected. However, the neurologic involvement may occur long before the onset of systemic symptoms, and oftentimes sarcoid is not included in the differential diagnosis. Involvement of the nervous system poses a difficult diagnostic problem for the clinician unmasking previously occult sarcoidosis (9). MRI is the investigation of choice in detecting parenchymal changes in the brain of patients with sarcoidosis (10). It has been reported that MRI has high sensitivity and specificity for evaluation of neurosarcoidosis (9–11). Involvement of the nervous system can range from peripheral or cranial neuropathy to CNS disease (12,13).

Physicians need be aware that sarcoidosis can present initially with a neurologic-ophthalmic manifestation. MRI of the brain or orbits is the best choice for initial imaging study. If sarcoidosis is suggested by the MRI findings, which may include lacrimal gland, meningeal
or hypothalamic enhancement, and pituitary stalk involvement, then a focused diagnostic evaluation is indicated. We recommend that CXR, anergy panel, PPD, ACE, gallium scan, and spinal tap be performed, although LP is more frequently abnormal in cases of anterior visual pathway disease than in this series. PFTs and 24-hour urine calcium were not helpful in identifying cases of sarcoidosis; it appears that they are useful in cases of anterior visual pathway disease (Frohman, Unpublished data).

Computed tomography scan of the chest may prove to be a useful adjunct. Kosmorsky et al. (15) presented a series of elderly white women with bilateral chronic uveitis. All had a negative CXR. Chest CT showed mediastinal lymphadenopathy in all cases, which led to ultimate histologic confirmation of sarcoidosis, although it may identify the same cases that gallium scan identifies.

Systemic corticosteroids are the mainstay of therapy and should be given to all cases with acute neurologic involvement. Other immunomodulatory agents such as cyclosporine may be effective in refractory cases or when the patient cannot tolerate the dose of corticosteroids required to control the disease process. Because cyclosporine has specific inhibitory effects on monocyte and T-cell activation via decreased interleukin-1 and interleukin-2, blocks B-cell activation, and improves hyperglycemic control, it should be an effective therapeutic agent for refractory sarcoidosis. Low-dose cyclosporine is a safe and effective therapeutic alternative in granulomatous disease (16). Others used azathoprine, cyclophosphamide, chlorambucil, and methotrexate as alternative treatment (17). In our series, neuro-ophtalmic symptoms, when treated acutely, generally responded well to therapy.

REFERENCES
Rancho Mirage, California
February 18–22, 2001

PLATFORM PRESENTATIONS

BILATERAL ORBITAL CONGESTION IS A RISK FACTOR FOR CORTICAL VENOUS DRAINAGE IN CAVERNOUS SINUS AREA DURAL AVMS

H. Stiebel-Kalish, A. Setton, A. Berenstein, M. J. Kupersmith; Petah Tikva, Israel

Background: Dural arteriovenous malformations (dAVM) that drain into cortical veins have increased risk of developing central nervous system dysfunction due to local venous hypertention, intracerebral hemorrhage or cerebral venous infarct.

Objective: We attempted to find whether a specific clinical sign might predict which patients have cortical venous drainage of dAVM in the region of the cavernous sinus (CSDAVM). We hypothesized that because of associated extensive thrombosis in the cavernous sinus, bilateral orbital signs should be a significant risk factor.

Methods: The records of 118 patients with CSDAVM were evaluated for the clinical features of the disorder and the results were correlated with presence of cortical venous drainage (CVD) identified by cerebral angiography or contrast-enhanced high-resolution magnetic resonance imaging (MRI) using Chi square test.

Results: 28 patients had some degree of bilateral orbital signs, 12 (43%) of whom had CVD and 16 without CVD. Bilateral orbital congestion was significantly associated with presence of CVD (p = 0.0005, RR 3.9). 40 patients had cranial nerve dysfunction (p = 0.0005, RR 3.9). 40 patients had cranial nerve dysfunction (p = 0.49), choroidal effusion (p = 0.23), optic neuropathy (p = 0.49), chorioidal effusion (p = 0.23), optic neuropathy (p = 0.69), subjective bruit (p = 0.12), objective orbital bruit (p = 0.75) or objective retro-aurocular bruit (p = 0.33) correlated with presence of CVD.

Conclusions: Patients who present with or develop bilateral orbital congestion or cranial nerve dysfunction should be recognized as being at increased risk for CVD. At the very least, a contrast enhanced high resolution MRI should be performed to look for CVD. If CVD is found, cerebral angiography and endovascular closure of their AV shunt should be considered.

SELF-REPORTED VISUAL DYSFUNCTION IN MULTIPLE SCLEROSIS: NEW DATA FROM THE VFQ-25

L. J. Balcer, S. Ma, D. A. Jacobs, C. E. Markowitz, S. L. Galetta, M. G. Maguire; Philadelphia, PA

Background: Despite the high prevalence of visual impairment in multiple sclerosis (MS), the usefulness of standard vision-specific quality of life measures, such as the 25-Item National Eye Institute Visual Function Questionnaire (VFQ-25), has not been determined for clinically heterogeneous MS cohorts.

Objective: The primary aim of this study was to examine VFQ-25 scores in a large cohort of MS patients and to determine construct validity for the VFQ-25 in patients with MS. The relation of VFQ-25 composite scores to ambulation status in MS was also examined.

Methods: As part of an ongoing study to develop an MS-specific vision questionnaire, the VFQ-25 was administered to 80 patients with MS using an interview format. Binocular visual acuities were obtained using ETDRS charts (3.2 meters).

Results: Compared with those of a published eye disease-free reference group (n = 118), VFQ-25 scores were significantly lower (worse) in our MS cohort (composite score and 10/12 sub-scales, p = 0.0001-0.009, two-tailed t-tests). These differences were observed despite the younger age of the MS cohort (mean 43 years for MS vs. 64 for reference group). Median disease duration was 2.5 years (0-30), and the median binocular visual acuity was 20/16 (20/12.5-20/250). Rank correlations of VFQ-25 composite scores with visual acuity were modest but significant (rS = 0.33, p = 0.003), supporting construct validity for the VFQ-25 in MS. Ambulation status did not predict VFQ-25 composite scores to a significant degree, even when accounting for patient age and disease duration (Wald test, p = 0.29-0.63) (0.92-0.63).

Conclusions: Patients with MS have a high degree of self-reported visual dysfunction that is not entirely captured by visual acuity or ambulation status. The VFQ-25 is an effective measure for capturing visual loss in MS, and should be used to complement visual function outcome measures in MS populations.

Supported by NIH grant EY 00351.

THREE-DIMENSIONAL KINEMATICS OF BLINKS IN HUMANS

O. Bergamin, S. Bizzarri, D. Straumann; Zurich, Switzerland

Background: So far, most studies on eye movements during blinks were restricted to rotations about the horizontal and vertical axes. Two phases have been identified: an initial downward and inward rotation and, with prolonged lid closure, an optional secondary upward and outward rotation (= Bell phenomenon).

Objective: We hypothesized that the initial eye movement during blinks is related to a pulse innervation of the inferior rectus muscle triggered by the omnipause neurons.

Supported by NIH grant EY 00351.
Muscle, indicating sixth nerve palsy. Mean vertical deviations during static head tilt to either side. Static OCR gains were subnormal, with a gain of 0.12 in both light and dark (p < 0.02).

Results: The initial eye movement during blinks consisted of a pulse in a direction that was always extensional, downward, and inward, irrespective of the duration of lid closure. Typically, the beginning of all three movement-components preceded the eyelid movement, thus a coil artifact is unlikely. During eyelid opening after 0.83s or 1.67s eyelid closure, a pulse of three-dimensional eye movements occurred in the opposite direction.

Conclusions: During the initial phase of eyelid closure, the eyes move in a direction that is consistent with a pulse-like activation of the inferior rectus muscle. We hypothesize that this pulse reflects downward premotor burst activity that, besides increasing the firing rate of the inferior rectus muscle, drives the firing rate of the levator palpebrae into inhibitory cut-off.

Vertical Misalignment and Static Ocular Counter Roll in Unilateral Sixth Nerve Palsy
A. M. F. Wong, D. Tweed, J. A. Sharpe; Toronto, Ontario

Background: Our preliminary clinical observations suggested that patients with isolated sixth nerve palsy could present with a small hypertropia.

Purpose: To determine the magnitude of vertical deviation and static ocular counter-roll (OCR) gain in patients with unilateral sixth nerve palsy.

Methods: Twenty patients with peripheral palsy, 7 patients with central palsy caused by brainstem lesions, and 10 normal subjects were studied. A history of eyelid movement, thus a coil artifact is unlikely. During eyelid opening after 0.83s or 1.67s eyelid closure, a pulse of three-dimensional eye movements occurred in the opposite direction.

Conclusions: During the initial phase of eyelid closure, the eyes move in a direction that is consistent with a pulse-like activation of the inferior rectus muscle. We hypothesize that this pulse reflects downward premotor burst activity that, besides increasing the firing rate of the inferior rectus muscle, drives the firing rate of the levator palpebrae into inhibitory cut-off.

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Conclusions: During the initial phase of eyelid closure, the eyes move in a direction that is consistent with a pulse-like activation of the inferior rectus muscle. We hypothesize that this pulse reflects downward premotor burst activity that, besides increasing the firing rate of the inferior rectus muscle, drives the firing rate of the levator palpebrae into inhibitory cut-off.

Conclusions: The small vertical deviation in peripheral and central palsy was consistent with hyperphoria that become manifest in the presence of esotropia. OCR gain was subnormal in both groups of patients. Disruption of the otolith-ocular reflex pathway may explain the vertical strabismus and subnormal OCR gain in central palsy.

Contrast Letter Acuity in Hereditary and Non-hereditary Ataxias

Background: Although visual complaints are common in patients with hereditary ataxias, systematic measures for readily evaluating visual function have not been ascertained.

Objective: To characterize the visual function of patients with hereditary and non-hereditary ataxias using the Low-Contrast Sloan Letter Charts (LCSLC).

Methods: Subjects included patients with hereditary autosomal dominant ataxias (ADA) (SCA 1, 2, 3, 7, 8, 9, others), ataxia-telangiectasia (Friedreich ataxia), sporadic ataxia (most commonly multiple system atrophy), hereditary spastic paraparesis (HSP), and visually- and neurologically asymptomatic volunteers.

Binocular LCSLC scores were based upon the numbers of letters read correctly (letter scores) at high contrast (visual acuity) and at 5%, 1.25%, and 0.6% contrast levels (low contrast).

Results: Patients with Friedreich ataxia and ADA demonstrated lower (worse) mean letter scores on the LCSLC compared with asymptomatic controls (Wilcoxon rank-sum test)

<table>
<thead>
<tr>
<th>Disease type</th>
<th>High contrast</th>
<th>5% contrast</th>
<th>1.25% contrast</th>
<th>0.6% contrast</th>
<th>P-value vs controls (sum of 4 charts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedreich</td>
<td>56 ± 1</td>
<td>45 ± 3</td>
<td>24 ± 3</td>
<td>13 ± 3</td>
<td>0.0029</td>
</tr>
<tr>
<td>ADA</td>
<td>44 ± 3</td>
<td>33 ± 5</td>
<td>20 ± 5</td>
<td>6 ± 3</td>
<td>0.0029</td>
</tr>
<tr>
<td>Sporadic</td>
<td>44 ± 3</td>
<td>34 ± 5</td>
<td>13 ± 5</td>
<td>4 ± 3</td>
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</tr>
<tr>
<td>HSP</td>
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<td>48 ± 3</td>
<td>30 ± 3</td>
<td>16 ± 6</td>
<td>0.051</td>
</tr>
<tr>
<td>Control</td>
<td>60 ± 1</td>
<td>57 ± 1</td>
<td>42 ± 2</td>
<td>33 ± 1</td>
<td></td>
</tr>
</tbody>
</table>

The most affected group was SCA7, consistent with the pigmentary retinal degeneration of this disorder. However, the difference in letter scores was still significant between ADA and controls, even with exclusion of the SCA7 patients. For each disease, greater differences between asymptomatic volunteers and patients were noted at lower contrast levels.

Conclusions: The present data suggest that LCSLC may be used to capture visual dysfunction in patients with degenerative ataxia. Further studies will investigate the anatomic components and disease features that correlate with decreased low contrast letter acuities.

Magnetic Resonance Diagnosis of Congenital Hypopituitarism in Children with Optic Nerve Hypoplasia
P. H. Phillips, M. C. Brodsky; Little Rock, Arkansas

Purpose: To determine whether structural neurohypophyseal abnormalities can be used to diagnose hypopituitarism in children with optic nerve hypoplasia.

Methods: Retrospective analysis of 67 children with optic nerve hypoplasia who had high resolution cranial magnetic resonance imaging and endocrinologic evaluation at Arkansas Children's Hospital from 1989 to 1999.

Results: In the 26 children with pituitary hormone deficiency, T1-weighted sagittal magnetic resonance imaging showed posterior pituitary ectopia in 16 cases, absence of the pituitary
infundibulum and posterior pituitary bright spot in seven cases, and a normal neurohypophysis in three cases. In all 41 children with normal endocrinologic function, magnetic resonance imaging disclosed a normal neurohypophysis.

**Conclusion:** Neurohypophyseal abnormalities, as disclosed by magnetic resonance imaging, can be used to direct endocrinologic referral in children with optic nerve hypoplasia.

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**DYSLEXIA: A VISUAL PROBLEM?**

S. Trauzettel-Klosinski, M. Mackeben, J. Reinhard, A. Feucht, U. Duerrwaechter, G. Klosinski; Tuebingen, Germany

**Background:** The cause of dyslexia is controversial; hypotheses are based on a deficit in central auditory processing, an impairment of the magnocellular system of the visual pathways and oculomotor control deficits. The analysis of eye movements provides information not only about the oculomotor system, but also about deficits in perception and information processing.

**Objective:** To differentiate potential deficits in pure oculomotor tasks (fixation stability, 5 saccades), in a logographic task (pictogram naming) and a phonologic task (reading), by assessing the scanning strategies under direct fundus control in a pilot study.

**Methods:** 14 dyslexic and 12 normally reading children were examined by a Scanning Laser Ophthalmoscope (SLO), which allows a direct monitoring of the fovea position during fixation of different stimuli and during reading aloud text and pictograms. Naming time for single pictograms was determined by the time between the fovea landing on the pictogram and the beginning of the speech.

**Results:** No differences between the groups were found regarding fixation stability of a single fixation cross and after 5 saccades. During reading texts, reading speed was highly decreased in dyslexics. However, during naming pictograms, we found two subgroups: children with prolonged pictogram naming times and others, who were as fast as the controls.

**Conclusions:** The dyslexic children showed significant differences compared to the controls, when written language was presented, whereas they were equal to the normals in isolated fixation tasks and some of them also in pictogram naming. This shows that the children examined in this study had no primary oculomotor disability, but a deficit in language processing. The two subgroups regarding pictogram naming time indicate a parallel processing of pictorial and linguistic stimuli. The SLO allows a subtle and precise analysis of the reading process and the picture naming, which provides valuable information about linguistic and visual information processing.

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**RU-486 (MIFEPRISTONE) AND MENINGIOMAS**

S. C. Benes, H. Newton, S. Scott, M. A. Sivick; Columbus, Ohio

Eleven patients with visual complaints had subtotal resections of meningiomas. They chose oral Mifepristone (RU-486) therapy rather than radiation, repeated surgeries, hydroxyurea or watching and were followed prospectively. Five were in a randomized SWOG protocol, 6 treated compassionately (not randomized). Serial MRI scanning every 6 months showed 1 with tumor shrinkage (24 months), 8 with stable non-growth (3, 4, 14, 20, 50, 64, 68, and 77 months), and 2 with growth (4, 6 months). Serial exophthalmometry, visual acuities and fields revealed clinical responses: 2 patients with radiologic growth ceased RU-486 after 4 and 6 months and later died; 2 had initial continued decline in vision and symptoms for 2 and 7 months then stabilized over the next 4 and 14 months; 7 had stable or slightly improved vision (1–2 lines) but improvement in their proptosis, redness, pain, headache, overall comfort or well-being. Due to temporary unavailability of the drug, three patients had 2, 6, and 6 month interruptions in RU-486 treatment and experienced: rebound pain, redness, proptosis, eyelid edema, headache and visual darkening (1), decreased vision but increased pain (1), and decreased vision (1). Their symptoms reversed when the drug was restarted. Adverse reactions included hot flashes (2), breast tenderness and slight gynecomastia (1), decreased appetite and weight loss (1), new unilateral headache and eye aches (1), hair loss (1), nightmares during naps (1), chronic blepharitis (1), and the rebound of pain and swelling symptoms upon discontinuance of the drug (3). Three of the 9 living patients chose radiation therapy (2) and further surgery (1) after 14, 20 and 42 months of RU-486. The other 6 continue RU-486 at this time. Nine of 11 patients believe the RU-486 provided them clinical stability, fewer surgeries, fewer doctor’s visits and time to think and research the field. Four patients publicly fought to retain access to RU-486 in the USA anti-abortion controversy.

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**PORTABLE PUPILLOGRAPHY OF THE SWINGING FLASHLIGHT TEST TO DETECT AFFERENT PUPILARY DEFECTS**


**Background:** Previously we found, using six light swings and monocular recording, that pupillography was not efficient enough to screen for mild afferent pupil defects (APDs).

**Objective:** To investigate the ability of a portable (Windows based) pupillometer, using binocular recording of the swinging flashlight test (SFT) for 20 seconds, to detect APDs.

**Methods:** Pupillary response curves (both eyes) of healthy volunteers (n = 22) with and without simulated APDs (created with neutral density filters (NDF)), and of abnormal patients (n = 21) with clinically graded APDs, were recorded. The light stimulus (0.2 sec or 2 sec duration) alternated (1 sec or 0.4 sec interval) between both eyes, simulating the SFT. Constriction amplitude, velocity and pupillary release were calculated by computer algorithm. In patients with APDs, NDFs were used to neutralize inter-eye differences.

**Results:** Significant correlation (Pearson coefficient 0.74, 0.77) between NDF strength and inter-eye differences was seen for diameter and velocity in simulated APDs. All abnormal patients (15/15) with APDs greater than 0.5 log units could be distinguished from normal (95% specificity). Pupillography was able to quantify APDs in all 21 abnormal patients when NDFs were used to neutralize inter-eye differences. Inter-eye variability in some normals prevented confident distinction of abnormal patients with 3 log unit APDs, from normal patients with large inter-eye differences. Using a .3 log unit NDF to accentuate or reduce inter-eye differences, stable APDs were predicted in 5/6 patients with possible APDs on clinical examination. Amplitude and velocity measurements were more accurate than pupillary release for all comparisons.

**Conclusions:** Using a 20 second, binocular recording of the SFT, this pupillometer identifies all patients with > 6 log unit APDs. With the addition of NDFs to reduce inter-eye differences, all patients with APDs can be accurately identified and quantified. Variability in some normals makes them indistinguishable from patients with subtle APDs.
ANALYSIS OF THE RETINAL NERVE FIBER LAYER IN PATIENTS WITH OPTIC NEUROPATHIES
K. P. Cockerham, R. Sudesh; Pittsburgh, Pennsylvania

Background: The Heidelberg Retinal Tomograph II (HRT) measures the birefringence of the retinal nerve fiber layer (RNFL). The computer model provides indirect measurements of optic disc area, area, volume, height variation contour, mean RNFL thickness, RNFL cross sectional area, reference height contour, rim and total nerve fiber layer thickness that are applicable to analysis of optic nerve swelling and atrophy seen in neuro-ophtalmology patients. Other parameters that target glaucoma cup-to-disc analysis are also provided.

Objective: To evaluate the efficacy of HRT in patients with different dysfuncions.

Methods: Thirty-five patients with afferent dysfunction had complete neuro-ophthalmic examination performed to include visual field testing. Diagnoses included ischemic optic neuropathy, optic neuritis, traumatic optic neuropathy and compressive optic neuropathy. The HRT data collection was limited to visual fields less than 20/4000, difficulty with fixation or significant media opacification were excluded due to machine limitations.

Results: The HRT was successfully performed in twenty-five patients. The objective information obtained from the HRT augmented the subjective visual field data. In three patients, all with bilateral afferent dysfunction, the HRT demonstrated an asymmetry in the retinal nerve fiber layer not identified with visual field testing.

Conclusions: HRT may provide useful objective information that augments a complete neuro-ophthalmic examination and visual field testing. HRT is not possible if central vision is poor, fixation instability is present or significant media abnormalities occlude imaging. We plan to compare serial HRT to visual field testing in patients with known optic neuropathies to assess whether the HRT is more sensitive to change.

NORMAL ERYTHROCYTE SEDIMENTATION RATE IN BIOPSY PROVEN GIANT CELL ARTERITIS
W. T. Cornblath, Ann Arbor, Michigan

The diagnosis of giant cell arteritis (GCA) can be very difficult to make and decisions to treat or not to treat can have far-reaching consequences. One standard test used in the diagnostic process is the Westergren erythrocyte sedimentation rate (WESR). However, the reliability of this test is unclear, with widely varying results being reported. In addition, the range of normal in elderly patients is also disputed, with 20, 40, or age divided by 2 all being used as the upper limit of normal. Our objective was to determine the range of WESRs in a large group of patients with biopsy proven GCA. We reviewed the charts of all patients with a biopsy proven diagnosis of GCA seen at the University of Michigan in a 10 year period. Ninety-six patients were seen with complete data available on 79. There were 12 men and 67 women. Age ranged from 61 to 86 (average 74), and from 55 to 93 for women (average 73). Five percent of patients (4/79) had an ESR below 20 (normal range 0-20). Twenty percent of patients (16/79) had an ESR below 40. Twenty-three percent of patients (18/79) had an ESR less than the age divided by 2 (for males), or age divided by 2 plus 5 (for females). ESRs less than 40 occurred between ages 63 and 85. In conclusion, relying on an elevated WESR to decide the presence or absence of GCA will exclude anywhere between 5% and 23% of patients, depending on what upper limit of normal is defined. As usual in neuro-ophthalmology an astute clinician must evaluate laboratory results in the context of the whole patient.

DIFFUSION-WEIGHTED MR IMAGING IN THE SHAKEN-IMPACT BABY SYNDROME

Introduction: Shaken impact baby syndrome (SIBS) is characterized by subdural hematoma (SDH), occipital bone fractures and retinal hemorrhages. Diffusion-weighted MR imaging (DWI-MRI) has recently proven useful in the diagnosis of acute cerebral ischemia and is more sensitive than conventional MRI to detect diffuse axonal injury from head trauma. In this study we evaluated the role of DWI-MRI in the diagnosis and management of children with suspected SIBS.

Methods: Retrospective review of medical records and neuroradiology findings of all children less than 2 with confirmed or suspected SIBS admitted to a Children’s Hospital. Only children who had an ocular examination by an ophthalmologist, and a brain MRI with DWI were included.

Results: Twenty-six children (14M/12F, mean age 7.1 mo [6 wk-24 mo]) were included. SIBS was confirmed in 18 children. All had SDHs. Ten had associated long bone fractures. Eighteen patients had diffuse retinal hemorrhages (unilateral in 3, bilateral in 15) associated with vitreous hemorrhage in 1. None of the patients died, but the short-term prognosis was poor in 19 children. Seven of the 8 cases without retinal hemorrhages had isolated SDH without parenchymal lesions on both conventional and DWI-MRI. The short term prognosis was excellent in 6 of them. In only 1 case with normal fundus was SIBS confirmed. Among the 18 patients with retinal hemorrhages, SIBS was confirmed in all but 1 case. All 17 patients with retinal hemorrhages and confirmed SIBS had an abnormal DWI-MRI. In 13 of them, DWI showed lesions that were larger than on conventional MRI.

Discussion/Conclusions: In all but 1 case with confirmed SIBS, the DWI-MRI was abnormal, suggesting diffuse cerebral injury associated with SDHs. In all other cases, DWI-MRI was normal. When DWI showed additional lesions not seen on conventional MRI, the short-term prognosis was poorer. DWI helps differentiate infarction from diffuse axonal injury, which may have implications regarding the acute management of children with SIBS. DWI-MRI may also provide better information about the timing of injury, which may help to determine the sequence of events and identify potential perpetrators.

FREQUENCY DOUBLING PERIMETRY IN NEURO-OPTHALMOLOGIC DISORDERS: A COMPARISON WITH CONVENTIONAL AUTOMATED PERIMETRY
M. Wall, R. Neahring, K. Woodward; Iowa City, Iowa

Purpose: Frequency doubling technology perimetry (FDT) was developed as a screening test for glaucoma. It is now used as a general visual screener. Patients with damage to the sensory visual pathways have different patterns of visual loss than glaucoma patients. Our aim, therefore, was to determine the sensitivity and specificity of FDT as a screening test compared with conventional automated perimetry (CAP) in neuro-ophtalmologic disorders and also to evaluate the extent to which FDT may isolate the My cells.

Methods: We tested 42 subjects from the general population recruited by randomly calling phone numbers from a phone book and 96 subjects with neuro-ophtalmologic disorders. Twenty-four patients had hemianopsia. All subjects were tested with both FDT and CAP. The tests were compared based on total deviation probability plot abnormalities for test loci com-
THROMBOPHILIA AS RISK FACTOR FOR CENTRAL AND BRANCH ARTERY OCCLUSION WITHOUT EVIDENCE OF EMBOLIC ORIGIN

R. Huna-Baron, O. Salomon, J. Moisseiev, U. Seligsohn, Tel Hashomer, Israel

Objective: To assess the prevalence of acquired and inherited thrombophilias in patients with central and branch retinal artery occlusion without embolic origin.

Methods: The study group comprised 21 consecutive patients with retinal artery occlusion (RAO) and 243 healthy subjects. All patients underwent Doppler ultrasonography of the carotid arteries and transthoracic or transesophageal echocardiography. Laboratory methods included polymerase chain reaction and restriction analysis for detection of factor V G1691A, factor II and/or hypercholesterolemia seven (50%) had a high titer of IgM antiphospholipid antibodies.

Results: Nine of the 21 (43%) patients had at least one thrombophilic marker: four were homozygous for MTHFR C677T, one was heterozygous for factor V G1691A, one had a high titer of IgM antiphospholipid, two were heterozygous for factor V G1691A and homozygous for MTHFR C677T, and one had lupus anticoagulant, a high titer of IgM antiphospholipid, homozygosity for MTHFR C677T and hyperhomocysteinemia. An interaction between vascular risk factors and thrombophilias seems important since out of 14 patients with hypertension, diabetes, and/or hypercholesterolemia seven (50%) had a thrombophilia. Analysis of the data disclosed that homozygous MTHFR 677T was a significant risk factor with odds ratio of 3.18 (95% CI 1.20–8.47). The prevalence of factor V G1691A was also higher in the RAO patients with odds ratio of 2.36 (95% CI 1.03–5.38), but it did not reach statistical significance probably due to the small sample size.

Conclusions: The results suggest that acquired and inherited thrombophilias are contributory risk factors in non-embolic RAO.

CHARACTER COUNTING USING SNELLEN EYE CHART TO ESTIMATE VISUAL ACUITY

A. H. Levy, T. J. McCulley, B. L. Lam: Miami, Florida

Purpose: To evaluate the usefulness of estimating visual acuity based on the ability to count the number of letters on the Snellen visual acuity chart so that this method may be used in patients with non-organic visual loss or cognitive dysfunction.

Method: The right eyes of 35 healthy adults with visual acuity of 20/30 or better were fogged with phoroptor plus lenses at random 0.25 diopter intervals (from +0.25 to +4.25 spheres) and tested with the popular standard projected Snellen visual acuity chart (Reichert 11180). Visual acuity and counting acuity were assessed repeatedly under various degree of fogging. Counting acuity was defined as the smallest line that the subject could count the number of letters correctly. Visual acuity was fogged to a maximum of 20/200.

Results: The number of subjects for each counting acuity level varied as each subject was not fogged to all levels of visual acuity. For each counting acuity level, the corresponding median visual acuity and the rounded upper 95% confidence interval are given below. The upper 95% confidence interval of the visual acuity represents the minimal visual acuity needed to attain the specific level of counting acuity. A close correlation was found between visual acuity and counting acuity, and in general, counting acuity was approximately 3 lines better than the median visual acuity.

<table>
<thead>
<tr>
<th>Counting acuity</th>
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<th>Visual acuity (median)</th>
<th>Visual acuity</th>
</tr>
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<tr>
<td>20/200</td>
<td>17</td>
<td>20/25</td>
<td>20/30</td>
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<tr>
<td>20/100</td>
<td>17</td>
<td>20/200</td>
<td>20/200</td>
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</tbody>
</table>

Conclusion: Our data suggests that the ability to count the number of letters on the Snellen visual acuity chart is a valid method in estimating visual acuity which may be used in patients with non-organic visual loss or cognitive dysfunction. C.R. None.

NON-ARTERITIC ISCHEMIC OPTIC NEUROPATHY IN PATIENTS WITH FACTOR V LEIDEN MUTATION

A. R. Harrison, J. D. Wirtshafter: Minneapolis, Minnesota

Background: The factor V Leiden deficiency is a recently described mutation leading to thrombosis. Previous studies have not determined whether factor V Leiden mutation is a risk factor for, modulator of, or unrelated to nonarteritic ischemic optic neuropathy (NAION).

Objective: Review the findings in patients with NAION with factor V Leiden mutation.

Methods: Retrospective case review.

Results: Three patients were identified who had NAION and factor V Leiden mutation. Two patients were under 40 years of age. Two patients had bilateral disease. Visual acuity was better than 20/40 on last visit in all affected eyes. Magnetic resonance
imaging of the brain and orbits was normal in 2 patients and in 1 patient showed multiple T2 hyperintensities.

Conclusions: Prospective studies are needed to determine if Factor V Leiden deficiency is (1) a causative or risk factor for NAION and (2) if Factor V Leiden mutation modulates the clinical presentation of NAION.

CAN SITA FAST BE USED AS A RELIABLE ALTERNATIVE TO GOLDMANN PERIMETRY IN NEURO-OPHTHALMIC PRACTICE?
G. Szatmary, V. Biousse, N. J. Newman; Atlanta, Georgia

Objective: To assess the potential role of SITA Fast (SF) computerized static perimetry compared with Goldmann manual kinetic perimetry (GVF) to reliably detect visual field defects in neuro-ophthalmic practice.

Background: Automated visual field tests may be a challenge in patients with severe neurological disease or poor visual acuity. In these patients, GVF is often preferred but is not often available and requires a skilled technician. The recent development of the SITA family of perimeters has allowed for shorter testing time without increasing test-retest variability in normal subjects and in glaucoma patients. However, its usefulness for detecting visual field defects in patients with neurological disease or severely decreased vision has not been evaluated.

Design/Methods: Prospective evaluation of 24 consecutive, neuro-ophthalmologically impaired patients with neurologic disability (Modified Rankin Scale [MRS] 3 or worse), or visual acuity 20/200 or worse in at least one eye. Goldmann and SF visual field tests were obtained on the same day. The two visual fields were compared with special attention to reliability, test duration, detection and quantification of neuro-ophthalmic visual field defects. Patients' test preference was subjectively assessed.

Results: Patients were separated into two groups, depending on their entry criteria. Group I: patients with moderate neurological disability but poor visual acuity (n = 14, 8 M, 6 W, mean age 51 [range 20-81]). Group II: neurologic disability of MRS 3 or worse (n = 10, 6 M, 4 W, mean age 54.8 [range 30-83]). GVF was reliable in 13/14 (93%) patients of group I and in 9/10 (90%) of group II, while SF was reliable in 13/14 (93%) patients of group I and in 7/10 (70%) of group II (NS). GVF and SF showed similar VF defects in 12/14 (86%) of group I and in 7/10 (70%) of group II (NS). Two patients from group II who had a full GVF, had diffuse non-specific changes and poor reliability parameters on SF. In one patient from group II with cognitive disorders, SF was not reliable and failed to demonstrate visual field defects related to bilateral parietal-occipital lobe lesions. The mean duration time for GVF in both eyes was 18.1 ± 4.6 minutes [range 11-25] in group I, and 15.4 ± 5.0 minutes [range 10-18] in group II, while for SF it was 10.7 ± 1.4 minutes [range 8.12-12.37] in group I and 11.5 ± 3.02 [range 7.45-16.55] in group II (p < 0.5). All patients preferred GVF testing.

Conclusion: SF strategy seems to be reliable and useful in most patients with neuro-ophthalmologic deficits associated with either severe neurological impairment or severely decreased vision. As opposed to full threshold perimetry, the shorter testing time and flexibility of SF likely reduce visual fatigue, one of the major limiting factors in the assessment of patients with neurogenic visual field defects. However, all our patients preferred GVF to SF testing.

SCANNING LASER POLARIMETRY FOR THE DETECTION OF NERVE FIBER LAYER DEFECTS IN PATIENTS WITH OPTIC NERVE DRUSEN
V. A. Khair, B. J. Katz, K. B. Digre, J. E. A. Warner, R. P. Harris; Salt Lake City, Utah

Patients with optic nerve drusen may have other diseases of the optic nerve, including glaucoma, complicating the evaluation of visualfield defects. In diseases of the optic nerve, visual field defects result from loss of ganglion cells and thinning of the retinal nerve fiber layer. We performed scanning laser polarimetry using the GDx Nerve Fiber Layer Analyzer on patients with optic nerve drusen in an attempt to determine if there were characteristic patterns of nerve fiber layer thinning unique to optic nerve drusen.

All patients had complete eye exams, automated perimetry, and ultrasound confirmation of drusen. We found that eyes with buried drusen showed neither visual field defects nor nerve fiber layer abnormalities. Eyes with visible drusen, but no visual field defect, had normal retinal nerve fiber layer parameters. Eyes with visible drusen and visual field defects always had nerve fiber layer abnormalities. We noted that the unaffected fellow eyes in patients with unilateral drusen had normal visual fields and normal nerve fiber layer thickness. The pattern of retinal nerve fiber layer abnormalities was not unique to optic nerve drusen and had many characteristics similar to the pattern seen in glaucoma. Scanning laser polarimetry provides an additional means of documenting and following retinal nerve fiber layer loss in patients with optic nerve drusen. However, this method may not provide a means of separating the nerve fiber layer loss of optic nerve drusen from that associated with other optic nerve diseases, including glaucoma. Further analysis of the data acquired by the laser polarimeter may, in the future, provide a means of specifically identifying nerve fiber layer loss caused by drusen. Because scanning laser polarimetry measurements reflect optic nerve damage, it provides an additional means of following optic nerve damage in optic nerve drusen patients who are unable to reliably perform.

TEMPORAL FIELD LOSS IN ‘UNAFFECTED’ EYE WITH ACUTE OPTIC NEURITIS: A LESION AT WILBRAND’S KNEE
M. J. Kupersmith, J. Straga, B. Zeiffer, R. Krager; New York, New York

Background: Recent work suggests that Wilbrand’s ‘knee’ is an artifact of longstanding unilateral optic nerve damage and the associated junctional scotoma is due to compression of the chiasm at multiple sites rather than a focal lesion where the posterior optic nerve enters the chiasm.

Objective: We investigated patients with optic neuritis involvement of the intracranial optic nerve to determine whether a junctional type scotoma can occur in an acute disorder without mass effect.

Methods: Retrospective analysis of patients with acute optic neuritis and no optic atrophy in either eye who had gadolinium MRI demonstrating abnormal enhancement of the intracranial optic nerve but not the chiasm. We also analyzed the presentation visual field data from the ONTT to determine the prevalence of temporal field loss in the second eye (previously unaffected).

Results: The signature case, a woman with painless loss of vision in one eye and a definite mild superior temporal field defect in the 2nd eye, was referred for MRI with a diagnosis of
pituitary adenoma but had posterior optic nerve enhancement. In our database of 92 patients with acute optic neuritis and gadolinium MRI, 14 had intracranial optic nerve enhancement, 8 cases met our MRI criteria and had visual fields done at the time of the MRI. We had 2 other patients who had concomitant involvement of the chiasm. Only 1 patient had the typical jux­tensional scotoma. In the ONTT data, 110/416 eyes without atrophy had 2nd eye abnormal visual fields. Two of these eyes had temporal field defects.

Conclusion: Jux­ensional scotoma in optic neuritis is uncommon. Due to the lack of exact localization, the ONTT data can not explain the anatomy. However, our case suggests that a jux­ensional scotoma can occur from a focal lesion in the posterior optic nerve and the ‘knife’ of Wilbrand may not be an artifact.

PARANEOPLASTIC OPTIC NEUROPATHY WITH EVIDENCE FOR VITREAL AND INTRATHECAL IN­FLAMMATION IN 8 PATIENTS WITH CRMP-5 NEU­RONAL AUTOANTIBODY AND LUNG CANCER
S. A. Cross, J. A. Mines, V. A. Lennon; Rochester, Minnesota

Background: Paraneoplastic optic neuropathy has been reported with lung carcinoma and incompletely defined autoan­tibodies: CRMP-5 autoantibody is specific for a newly recognized collapsin response-mediator protein in retina, small-cell carcinosmas and neurons. CRMP-5-IgG is a marker of neuro­logical autoimmunity with lung carcinoma or thymoma (Yu et al., Ann Neurol, v. 49, Feb. 2001).
Objective: To report ophthalmologic, neurologic and laboratory profiles of 8 patients with optic neuropathy. CRMP-5-IgG in serum or cerebrospinal fluid (CSF), and lung carcinoma.
Methods: The 8 patients were amongst 116 in whom paraneo­plastic autoantibody testing revealed CRMP-5-IgG. Clinical in­formation was obtained from records and physician interviews. All 116 had a neurological presentation; 90% had cancer.
Results: The 8 patients (5 males) were smokers. Small-cell carcinosmas was confirmed in 7, confined to the chest in 6: 1 had an unsuipipect chest mass. All had subacute visual loss, centro­central scotomata and/or acute deficits in visual fields, and swollen discs. Some fundi had nerve fiber layer hemorrhages. Fluorescein angiography showed nerve head hyperfluores­cence. The vitreous contained numerous small non-clumped cells (5/7). Diagnostic vitreectomy (2 patients) disclosed inflammatory reaction without evidence of lymphoma. MRI scans revealed no structural lesions in the visual pathway. Neurolog­i­cal accompaniments included cerebellar ataxia (4), dementia (3), myoclonus (1), chorea/dystonia (2), neuropathies (3 somatic, 4 autonomic), Lambert-Eaton syndrome (1) and altered taste and smell (4). Lumbar puncture (n = 5) revealed normal opening pressure, pleocytosis (7-32 cells, monocytes and immature forms), elevated protein and CRMP-5-IgG (2/5 positive, titer 1:500-1:10,000). Serum titer (7/8 positive) were <1:60 to 1:25,000, CSF was positive at 1:500 in the patient whose serum was negative, indicative of CRMP-5-specific T- and B-lymphocyte activity within the nervous system.
Conclusions: Optic neuropathy with the CRMP-5 autoanti­body marker is associated with inflammatory vitreous and CSF, intrathecal CRMP-5-IgG synthesis, multifocal neurological ab­normalities, and limited small-cell lung carcinoma.

OPTIC DISC CUPPING ALL OVER
K. Landau, B. Ghori; Zurich, Switzerland

Background: Various pathogenic mechanisms are known to produce optic atrophy. In many instances, diagnosis can be readily established by combining information from history, functional evaluation, clinical examination including assessment of optic disc morphology, and ancillary testing. Occasionally, a patient may present with a cupped optic disc remining of glaucomatous optic neuropathy in whom a different mechanism than glaucoma is responsible for the resulting op­tic neuropathy.

Objective: To present examples of cupped optic discs caused by a variety of insults other than glaucoma.
Methods: Over a period of 10 years the authors collected ex­amples of non-glaucomatous cupping of the optic disc in their neuro-ophtalmology and glaucoma services.
Results: We found patients with glaucomatous looking discs in almost every category of optic neuropathies. In some cases low tension glaucoma was the initial diagnosis that later had to be revised, but in most instances the authors were impressed by the development of optic disc cupping following entities such as demyelinative optic neuropathy, compression from suprasel­lular lesions, arteritic AION, central retinal artery occlusion, opt­ic nerve or chiasmal trauma, periventricular leukomalacia, dominant optic atrophy and toxic optic neuropathy.
Conclusion: Optic disc cupping is a non-specific sign of glau­comatous optic neuropathy. If additional clinical evidence is not characteristic of glaucoma and diurnal curve does not reveal increased intraocular pressure, a search for other causes is indicated. Most helpful parameters in distinguishing non­glaucomatous from glaucomatous cupping are the color of the remaining rim and the pattern of visual field damage.

References

EQUIVALENT DOSE ORAL STEROID USE IN OPTIC NEURITIS: READY FOR PRIMETIME?
R. D. Bailey, J. E. Carter, San Antonio, Texas

Background: Modifications of the Optic Neuritis Treatment Trial (ONTT) steroid protocol are commonly used in daily practice. During the 2000 North American Neuro-Ophthalmology Society (NANOS) meeting, a survey was conducted to determine whether the representative neuro-ophtalmologists would use doses of oral steroids equivalent to those employed in the ONTT. Discussions on NANOS-NET have explored using an oral dose equivalent to the intravenous dose employed intravenously in the ONTT.

Objective: To investigate the use of oral equivalent high-dose steroid regimens for treatment of optic neuritis.
Methods: A questionnaire was distributed during the poster session of the 2000 NANOS meeting.
Results: Eighty-eight surveys were returned during the meeting. Twenty-seven neuro-ophtalmologists routinely treat their ON patients with steroids, and an additional use steroids if the MRI shows white matter lesions. Forty-eight attendees did not answer the question regarding the proposed use of a high-dose oral regimen. Of the 40 who did respond, 30 would use an oral equivalent, nine would never use an oral equivalent, three responded don't know or need more information.
Conclusion: Among the neuro-ophtalmologists attending the 2000 NANOS meeting and responding to the questionnaire, there is no consensus on substituting a high-dose oral steroid
A COMPARISON OF MULTIFOCAL VEPs FROM PATIENTS WITH ACUTE ONSET OF EITHER ION OR OPTIC NEURITIS

J. E. Hong, J. G. Odel, X. Zhang, M. M. Behrens, D. C. Hood; Syracuse, New York

Background: Ischemic optic neuropathy (ION) and optic neuritis (ON) can sometimes be difficult to distinguish.

Objective: To record multifocal visual evoked potentials (mVEP) from patients with ION or ON during their acute phases.

Methods: Patients experiencing unilateral attacks of ION (n = 7) or ON (n = 8) were studied. Monocular mVEPs were obtained using a scaled, 60 sector, dartboard array [1]. Two 7-min. runs were obtained for each eye. A pseudo S/N ratio was obtained for each response based upon the two runs. Signals with S/N ratio <2 were omitted from the analysis. For each of the 60 pairs of monocular responses, the ratio of the RMS amplitudes was determined [1]. Implicit times were obtained using a cross-correlation method. Estimates of visual field changes in the 60 sectors of the mVEP array were interpolated from the visual fields [1,2].

Results: The relative loss in amplitude of the mVEP from the affected eye is correlated with field loss for both groups [r2 of 0.59 (ION) and 0.58 (ION)]. For field losses of 10 dB or less, the log of the ratio of the relative amplitude was linearly related to log field loss (i.e., dB values) for both ON (r2 = 0.70; slope = 0.67) and ION (r2 = 0.38; slope = 0.48). The implicit times for ON, but not ION, were significantly delayed and these delays correlated with field loss. However, only 4 of the patients with ON had reliable signals, 3 of these had one or more responses with a significant delay.

Conclusion: During the acute phase, in some cases ON can be distinguished from ION, but in others the mVEP responses are too small to allow measurement of implicit time. After recovery, ON can be distinguished from ION in many cases based upon prolonged implicit times [1,3].

References

PATIENTS WITH IDIOPATHIC INTRACRANIAL HYPERTENSION FREQUENTLY HAVE OTHER DEFINED HEADACHE DISORDERS

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Objective: To determine the following in patients with idiopathic intracranial hypertension (IIH): (1) the initial symptoms and (2) whether patients subsequently developed headaches that were classifiable by International Headache Society (IHS) criteria.

Methods: Medical records were reviewed from 1991–2000. Inclusion criteria were papilledema at presentation, normal brain neuroimaging study (except empty sella), and a lumbar puncture confirming an opening pressure > 250 mm water with normal CSF contents.

Results: Eighty-four patients (82 females, 2 males) between ages 16–59 (mean = 29) years met the criteria. At the onset of symptoms, patients described their headaches as pounding/drobbing (20), pressure (18), aching (17) and explosive (11). Ten patients did not have headache on presentation and no description of the pain was available in 16. Severity, location and frequency of head pain were variable. The most frequent accompanying symptoms were transient visual obscurations (38), intracranial noises (36), blurred vision (25), diplopia (16), scotomas (14), nausea/vomiting (13) and paresthesias (11). Eleven adults related a history of headaches since childhood: 3 migraine with aura (MWA), 3 migraine without aura (MWOA), 1 menstrually-associated headache, 2 chronic tension-type headache (CTTH), 1 episodic tension-type headache (ETTH), 1 “sinus” headache. Following the diagnosis of IIH, 15 patients (18%) had resolution of their headaches after the initial lumbar puncture. Fifty-six patients (67%) developed IHS classifiable headache disorders: ETTH (30), MWOA (29), plus 2 patients whose headaches were <4 hours long, CTTH (10), analgesic overuse headache (8), idiopathic stabbing headache (3), cluster headache (1), benign exertional headache (1). Only 1 patient developed MWA who did not have it pre-morbidly; however, she had a history of MWOA. Nineteen patients (23%) had more than one type of headache.

Conclusion: Patients with IIH usually have headaches during the course of their illness that may bear no resemblance to their presenting headache pattern. The most common headache types are ETTH and migraine without aura. Due to the retrospective nature of this study all headache types, especially analgesic rebound headache, are probably underestimated. Recognition and treatment of specific headache disorders is an important aspect of the care of patients with IIH.

MAR SYNDROME 64 PATIENTS, UPDATE 2001

J. L. Kelner, C. Thirkhill, P. Yip; Sacramento, California

Purpose: The purpose of this study is to evaluate the signs, symptoms, and immune response of patients with Melanoma-Associated Retinopathy (MAR) syndrome.

Methods: The clinical information and immunologic findings from UC Davis patients and the clinical information available on patients from the world’s literature were analyzed in a combined fashion.

Results: A total of 64 MAR syndrome patients (11 UC Davis patients and 53 from the world’s literature) have been studied. 36 patients had available age and gender information, showing 30 males and 6 females. The average age at onset of vision disturbance was 56.8 years (ranging from 30–78 years). 26.30 patients had good initial visual acuity at the time of presentation, ranging from 20/20 to 20/60. However, in 7:33 patients moderate to severe visual loss occurred in one or both eyes. Visual field findings included central scotomas, arcuate defects, and generalized constriction. Fundus examination was normal in 19/41 patients, 10/41 showed optic nerves pallor, and 11:41 had vessel attenuation. 9:41 patients were described as having moderate numbers of vitreous cells. Electretinograms (ERG) tested on 35 patients revealed congenital stationary night blindness (CSNB) patterns and ERG findings typical of MAR syndrome. The time from the diagnosis of melanoma to the onset of metamatic disease was an average of 3.6 years (ranging from 2 months to 19 years) in 28 patients. In 35
patients the time from the diagnosis of melanoma to the appearance of MAR syndrome averaged 3.8 years (ranging from 3 months to 17 years). The average survival time was 6.28 years. Surgery, chemotherapy, and immunologic and radiation therapy were used to treat the primary tumor and metastasis. Five patients had visual improvement with various treatment regimes. All patients studied produced auto-antibodies reactive with components of the bipolar layer. Those studies in this laboratory were also found to exhibit a variety of additional antigen-antibody reactions with different ocular components and in their Western blot reactions on extracts of retina.

Conclusion: The MAR syndrome demonstrates a greater diversity in the clinical and immunologic presentations than those previously considered.

THE EFFECT OF STIMULUS BRIGHTNESS ON THE SEPARATION OF PATIENTS FROM NORMAL SUBJECTS USING COMPUTER RECORDING OF THE PUPIL LIGHT REFLEX

R. H. Kardon, A. L. Bassman; Iowa City, Iowa

Background: Recent evidence from our studies of unilateral optic neuropathy has shown a greater relative afferent papillary defect (RAPD) with brighter light stimuli, which may indicate how damage may affect the neuronal firing properties of ganglion cells.

Objective: To determine if the brightness of the stimulus light used to determine the relative afferent papillary defect (RAPD) can influence the ability to differentiate normal subjects from patients with asymmetric visual loss.

Methods: Computerized infrared pupillography was performed on 53 normal subjects with normal visual field testing and 52 patients with asymmetric visual field loss. A 0.2 second light stimulus subtending a 30 degree radius visual field was alternately presented to the right and left eye every 3 seconds. At each of 10 different stimulus light intensities, the distribution of the asymmetry in pupil contraction (right eye stimulation-left eye stimulation) was compared between the normal and patient groups using an impaired t-test assuming unequal variance.

Results: There was a highly significant effect of stimulus brightness on the separation of the normal and patient groups (linear correlation of log p value vs. intensity: p < 0.001). Brighter stimuli produced a greater separation between the normal and patient group and this was also statistically significant when the patients were subdivided into those with mild, moderate, or severe damage.

Conclusions: A brighter stimulus light (short duration, under computer-control) causes a greater separation between normal subjects and patients with unilateral or asymmetric visual dysfunction. Our results indicate that disease of the afferent visual system impairs the pupil light reflex to a greater extent in patients compared to normal subjects when using a brighter light stimulus. This may have implications on how optic nerve damage affects the ability of ganglion cells to respond to light intensities near threshold (low neuronal firing rate) vs. suprathreshold (high neuronal firing rate).

LOCAL USE OF TRIAMCINOLONE IN DYSTHYROID ASSOCIATED OPHTHALMOPATHY


Objective: To study the local effects of intra-orbital triamcinolone in patients with DAO.

Study design: Prospective randomized unmasked-pilot study.

Methods: Fifty patients were included in this study from April 98 to April 99 with the following inclusion criteria: DAO of 6 months maximum, diplopia as the main complaint and completely free of treatment for ophthalmopathy regardless of the stage of dysthyroidism. Patients were randomized in 2 groups; G1, who received para-bulbar injections of 20 mgs of triamcinolone on each orbit every week, totaling 4 applications (per-orbit) and G2, a control group.

Diplopia was measured with a Goldmann perimeter. With both eyes open patients determined the area of non-diplopia which was calculated at week 0, 10 and 24. The thickness of extraocular muscles was measured with a caliper on CT coronal views at week 0 and 24.

Results: Thirty-seven patients completed this study (G1 n = 20, G2 n = 17). After 6 months G1 patients demonstrated improvements in the field of non-diplopia at week 10 (change: 91.56%, p = 0.054) and maintained the improvement at week 24 (change: 105.9%, p = 0.041). While in G2 we observed a tendency to deteriorate the non-diplopia area (2%, p = 0.6 and 1.3%, p = 0.84 at weeks 10 and 24 respectively). The thickness of extraocular recti improved dramatically in the injected group (change: inferior rectus: -13.21%, p = 0.001, medial rectus: -8.24%, superior rectus: -9.5%, p = 0.032, lateral rectus: -11.49%, p = 0.005) compared to the changes observed in controls (inferior rectus: -4.02%, p = 0.31, medial rectus: 0.56%, p = 0.89, superior rectus: 12.54%, p = 0.081, lateral rectus: -0.53%, p = 0.92). Non-undesirable local effects, due to the procedure, were observed out of few hematomas in the site of the injections.

Conclusions: Local injections of triamcinolone demonstrated an increase in the non-diplopia area and a decrease in the recti thickness, compared with the results obtained in the control group. Minimum local side effects, due to the injections, were observed. We favor the use of this treatment in patients with DAO.

LOCAL USE OF TRIAMCINOLONE IN DYSTHYROID ASSOCIATED OPHTHALMOPATHY DAO. Part II

Study design: Prospective randomized unmasked-pilot study.

Methods: 50 patients were included in this study from April 98 to April 99 with the following inclusion criteria: DAO of 6 months maximum, diplopia as the main complaint and completely free of treatment for ophthalmopathy regardless of the stage of dysthyroidism. Patients were randomized in 2 groups; G1, who received para-bulbar injections of 20 mgs of triamcinolone on each orbit every week, totaling 4 applications (per-orbit) and G2, a control group. Visual acuity (VA), ocular tension (OT), exophthalmos (EX), body weight (BW) and blood pressure (BP) were checked on week 0, 10 and 24. Laboratory data: Glycemia, calcemia, plasmatic and urinary Cortisol (PC and UC) were obtained at week 0 and 10 for each group. In G1, ocular corticol was also measured on week 3. BW and BP were measured on weeks 1, 2, 3 and 4.

Results: Thirty-seven patients completed this study (G1 n = 20, G2 n = 17). After 6 months, VA and OT did not vary in either group. EX improved in G1, being (-2.91 mm +/- 7.36 SD) at week 10 and (-1.76 mm +/- 10.06 SD) at week 24, while no significant changes were observed in G2 (1.52 mm +/- 5.94 SD at week 10 and 0.63 mm +/- 7.7 SD at week 24). Glycemia and calcemia as well as BW and BP remained within normal parameters in both groups during the study-period. Both PC and UC checked slightly below normal limits in G1, while remaining normal in G2.

Conclusions: Local injections of triamcinolone demonstrated no change in VA and OT, while amelioration in the EX level...
was observed compared with G2. Glycemia and calcemia were not altered as well as BP and BW. PC and UC were below normal range in G1. Due to the benefit in EX level, the absence of ocular or major systemic (unwanted) effects, we favor the use of this treatment in patients with DAO.

**POSTER PRESENTATIONS**

**INFRARED PUPILLOGRAPHY AND VISUAL EVOKED RESPONSE IN UNILATERAL HYPEROPIC AMBLYOPIA**

P-I. Chou, J-T. Chen; Taipei, Taiwan

**Background:** Unilateral hyperopic amblyopia has distinct clinical manifestations including unilateral hyperopia with early onset amblyopia. Determination of whether this type of amblyopia subserves different neuronal defects requires further investigation.

**Objective:** To evaluate the pupillary light reflex and visual evoked response (VER) in unilateral hyperopic amblyopia patients.

**Methods:** Infrared pupillography (IRP) and pattern VER were obtained for normal and fellow hyperopic amblyopic eyes in 21 young adults.

**Results:** The IRP initial diameter was significantly larger in the amblyopic eyes than in the normal eyes (p = 0.0479). Time to minimum diameter was delayed in the amblyopic eyes with statistical significance (p = 0.0453). Tp100 latency of pattern VER was significantly delayed in the amblyopic eyes (p = 0.001).

**Conclusion:** Both IRP and pattern VER were sensitive in detecting unilateral hyperopic amblyopia. Physiologic disturbance in the retinal level, mainly in the fovea area, together with a deficit in the paravascular layer of the lateral geniculate body is responsible for the visual acuity deficit in hyperopic amblyopia.

**BRÜCKNER’S REFLEX AND THE FOVEAL PIT: A RELATIONSHIP BROUGHT TO LIGHT**

C. F. Parsa, Baltimore, Maryland

Popularized by Brückner in 1962, the reason for the asymmetry of red reflexes in the test that today bears his name has eluded explanation. In practice, an ophthalmoscope or other paraxial light source is used to make a qualitative comparison between simultaneous light reflexes from both fundi as the patient fixates on a light source at arm's length. The presence of even a slight deviation of an eye, or of an asymmetry in refractive power, manifests as a brighter reflex in the non-fixing or unfocused eye and alerts the clinician to the presence of a strabismic or an anisotropic condition. Various hypotheses have been put forth in the past to explain this effect, invoking phenomena such as decreasing macular pigment density away from the fovea, off-axis optical aberrations, imperfect conjugacy of the retinal image of the light source with the observer eye, specular reflections from the retina, retinal backscattering of light, or a combination of the above. No conclusive evidence has been available to determine which, if any, of these hypotheses are correct. The use of a new optical model, however, demonstrates that it is in fact specular reflection from the parafoveal area which is the predominant factor, with other previously proposed factors producing perhaps only minor contributions. Such knowledge is important in the design and utilization of mass screening devices now being contemplated for the detection of predisposing factors for amblyopia in the pediatric population.

**TRANSIENT HORIZONTAL NYSTAGMUS IN INFANTS FROM DRUG-ADDICTED WOMEN: A WITHDRAWAL SYNDROME?**

F-X. Bonnat, M. Gaillard; Lausanne, Switzerland

**Background:** Horizontal pendular nystagmus is usually a benign isolated congenital disorder manifesting during infancy. Both its frequency and amplitude tend to decrease with age, but pendular nystagmus will remain present.

**Objective:** To report an unusual evolution of horizontal pendular nystagmus.

**Methods:** Three case histories.

**Results:** Three infants presented with the sudden onset of horizontal pendular nystagmus a few weeks after birth. All three infants were delivered from drug-addicted mothers who were actively abusing illegal substances during pregnancy. Apart from nystagmus, the three infants were healthy at the time of examination. Within a few months after the onset of ocular motility disturbance, the nystagmus disappeared in all three cases.

**Conclusion:** We postulate that the appearance of transient horizontal pendular nystagmus in infants born from drug-addicted women might represent a withdrawal syndrome.

**BOTULINUM TOXIN THERAPY FOR APRAXIA OF LID OPENING**

D. Boghen, V. Tozlovanu, A. Iancu, R. Forget; Montreal, Quebec

**Background:** Apraxia of lid opening (ALO) designates an intermittent inability to open the eyes voluntarily in the absence of apparent orbicularis oculi (OOc) contraction. Previous studies have suggested that clinically undetectable, but recordable activity of OOc plays an important role in ALO.

**Objective:** To verify the hypothesis that Botulinum toxin (BTX) injection in OOc will improve eye opening delays and clinical disability in ALO patients.

**Methods:** Lid movement and EMG activity of OOc were simultaneously recorded in twelve ALO patients (60 ±11 years) before and after BTX treatment. Patients' disability was measured before and after treatment by means of a "clinical disability index." The BTX injections were given at four sites in the pretarsal portion of the OOc. The subjects were asked to open the eyes "as fast as possible" in response to a sound signal and to keep them open (20 trials). The time latencies to the onset of eye opening and to complete the eye opening and the time during which eye opening was sustained were determined and correlated with OOc activity. The results of pre- and post-treatment evaluations were then compared.

**Results:** Following treatment, the time delay to complete eye opening (754 ± 207 ms) was significantly shorter than before treatment (1038 ± 385 ms); the latency to the onset of lid opening decreased from 441 ± 196 ms to 322 ± 55 ms; the time of sustained lid opening increased from 7543 ± 3194 ms to 10641 ± 3430 ms; the time delay to inhibit the OOc activity showed a strong tendency to decrease; the quantity of EMG during lid opening was significantly decreased; the clinical disability index showed a marked improvement in 10 out of the 12 patients.

**Conclusion:** In ALO patients, BTX treatment leads to an improvement of lid movement metrics and clinical outcome. This is best explained by a diminished activity of the hyperactive OOc.

**Grant provided by:** Fonds DesRecherche Besner Vakalis, University of Montreal.
THALIDOMIDE AS A STEROID-SPARING AGENT IN REFRACTORY NEUROSARCOIDOSIS
J. C. Callwood, S. Magaluri; New Orleans, Louisiana

Background: Sarcoid is a multi-system granulomatous disease of unknown etiology that is mediated by macrophages, activated T-cells and cytokines IL-2, IL-12, and TNF alpha. Neurosarcoid occurs in approximately 5-10% of patients. Corticosteroids are the primary treatment for neurosarcoidosis, however, one-third of patients are refractory to corticosteroids alone and may require a steroid-sparing agent. Thalidomide inhibits macrophages, T-cells and suppresses IL-2 and IL-12 and TNF-alpha.

Objective: We report our experience with the off-label use of thalidomide as a steroid-sparing agent in five cases of biopsy-proven refractory neurosarcoidosis.

Methods: Refractory neurosarcoid patients were selected from a clinical neuro-ophthalmology practice over the course of two years. Treatment with thalidomide was begun at a dose of 50 mg q.h.s. and increased by 50 mg as tolerated with an initial target dose of 200 mg and a secondary target dose of 400 mg per day. After baseline nerve conduction velocities (NCV), patients were monitored for compliance with birth control, side effects, clinical examinations, blood counts, and hepatic function. Neuroimaging and NCV were repeated at six months or with a change in clinical status.

Results: Thalidomide was well-tolerated by three of the five patients treated. One patient (Case #1) developed fever and thalidomide treatment was discontinued. No therapeutic effect was observed. Case #2 was titrated up to 400 mg per day of thalidomide with no visual improvement, but with complete resolution of pachymeningitis. Case #3 developed a rash following two weeks of thalidomide therapy and treatment was discontinued without therapeutic effect. In case #4 thalidomide was discontinued secondary to paresthesia, but repeat neuroimaging revealed a marked improvement of orbital mass and cavernous cord lesion. Case #5 tolerated the thalidomide well with minimal drowsiness. No therapeutic effect has been observed.

Conclusion: Thalidomide has a potential use as a steroid-sparing agent in refractory neurosarcoidosis, but warrants further study.

ISOLATED UNILATERAL POST-TRAUMATIC INTRACRANIAL OPPHTHALMOLPLEGIA
J. W. Chan, Las Vegas, Nevada

Internuclear ophthalmoplegia (INO) is an uncommon complication of closed head trauma. A review of the literature showed 13 documented cases. Of these only 4 were unilateral and 2 of them were associated with other neurological findings. I present an unusual case of isolated unilateral INO after blunt head trauma.

This 32-year-old man was assaulted by gangsters who hit and kicked the right side of his head. He had loss of consciousness for several hours. On examination he had a right mandibular fracture and right periorbital ecema. His corrected visual acuity was 20/20 in both eyes. Pupillary responses and Humphrey automated visual field testing were normal.

Ocular motility examination demonstrated orthophoria in primary position. His right eye was unable to adduct and his left eye had abduction nystagmus during leftward gaze. This nystagmus had a vertical and rotary component. He had no other associated neurological abnormalities. His MRI of the brain with contrast revealed a right medial longitudinal fasciculus (MLF) lesion. CSF studies confirmed no infectious or inflammatory processes, such as multiple sclerosis. After 4 months he had a mild adduction deficit in his right eye and mild diplopia on left gaze.

Isolated unilateral JNO is a rare complication of blunt head trauma. Possible mechanisms include an ischemic etiology in which the shearing forces within the brainstem compress the perforating arteries of the basilar artery to cause decreased blood flow to the MLF. Mechanical injury from stretching forces can also damage fibers of the MLF. Therefore, isolated JNO should be considered in the differential diagnosis when an acute head trauma patient presents with an adduction deficit.

QUANTIFYING MOTILITY DEFICITS BY ALTERNATE COVER, RED MADDOX ROD, AND GOLDMANN PERIMETER
A. Coleman, E. Eggenberger; East Lansing, Michigan

Background: Alternate Cover (AC) and Red Maddox Rod (RMR) tests have been used to measure deficits from cranial nerve palsies in prism dipters. The Goldmann perimeter has been used to measure duction limitations in degrees of motility. The correlation between duction limitations by perimeter and deficits measured in prism dipters has yet to be elucidated.

Objective: To determine the correlation between prism measurement obtained by AC or RMR testing and degrees of duction measured by the Goldmann perimeter.

Methods: Retrospective chart review on patients with sixth nerve palsies seen at Michigan State University Neuro-Visual Unit between July 1998 and August 2000. Inclusion criteria included patients with isolated unilateral sixth nerve palsy with measurements performed by the Goldmann perimeter and by either the AC or RMR on the same visit. The data was recorded as degrees of abduction by Goldmann and prism dipters in both primary gaze and abduction.

Results: A total of 25 patients yielded 35 measurement comparisons. The Pearson correlation coefficient between esotropia in primary gaze and abduction were 0.94508. The correlation coefficient between degrees of abduction and dipters of esotropia on abduction was -0.59173. The correlation coefficient between degree of abduction and esotropia in primary gaze was -0.55401.

Conclusion: The consistent correlation between measurements of unilateral motility deficits by Goldmann perimeter compared to the AC or RMR examinations supports the use of all three methods in quantifying motility defects.

INFRAORBITAL NERVE PALSY SECONDARY TO LASIK
Charles Efrig, T. McCulley, B. Lam, N. Schatz, S. Rosenfeld; Miami, Florida

Objective: To describe a case of infraorbital nerve palsy associated with laser in situ keratomileusis (LASIK).

Method: Case report.

Results: A healthy 46-year-old woman underwent bilateral LASIK on 11/18/99 for mild myopia (-2.00 OD, -2.25 OS). LASIK was performed on the right eye first without complications. During the procedure of the left eye, mild difficulty with seating of the suction cup was encountered due to a small palpebral fissure. During this maneuver, the patient experienced extreme knife-like left facial pain which was followed post-operatively by persistent numbness and tingling over a similar area. On postoperative day 5, she noticed twitching in the left corner of the mouth and the left upper eyelid, which subsequently resolved. Examination showed decreased sensation over the left cheek in the distribution of the infraorbital
nerve. The ophthalmic and neurologic exam was otherwise unremarkable. Brain MRI revealed rare small white matter lesions consistent with arteriosclerosis. CT of the orbits was unremarkable with an intact orbital floor. The patient was treated with gabapentin and nortriptyline followed by self-prescribed acupuncture therapy. One year postoperatively, symptoms have improved but numbness, tingling, and pain involving her left cheek has continued.

Conclusions: LASIK may rarely produce infraorbital nerve dysfunction, which to our knowledge has not been reported. Our case suggests that compression by the suction cup is the contributing factor.

OPTIC TRACT COMPRESSION FROM DOLICHOECTATIC BASILAR ARTERY
M. F. Gitigis, B. L. Lam, S. F. Falcone; Miami, Florida

Purpose: To report a case of optic tract compression due to a dolichoectatic basilar artery.

Method: Case report.

Results: A 74-year-old man with progressive loss of vision over 13 years and no other neurologic signs or symptoms was found to have bilateral optic nerve head pallor and a left homonymous hemianopia. Magnetic resonance imaging and angiography revealed a severe dolichoectatic basilar artery compressing the right optic tract.

Conclusion: Basilar artery dolichoectasia may rarely cause compression of the optic tract and progressive visual loss.

ACQUIRED ARNOLD-CHIARI-LIKE MALFORMATIONS AFTER LP SHUNTING IN PSEUDOTUMOR CEREBRI
S. C. Benes; Columbus, Ohio

Retrospective chart review of 300 patients with pseudotumor cerebri followed over 1 to 20 years found 245 female, 55 (18%) male. For those in whom baseline preoperative head scans were MRIs, only 3 had Arnold-Chiari Type 1 malformations (protrusion of the cerebellum tonsils below the level of the Foramen Magnum on sagittal section) at the time of diagnosis. These 3 have not undergone lumboperitoneal (LP) shunting in their care and have been medically managed (2) or undergone optic nerve sheath decompression surgery for medical failure to prevent progressive visual loss (1). However, 4 patients (all female) who had normal Foramen Magnum anatomy preoperatively developed Arnold-Chiari-like malformations after LP shunting. These occurred between 4 months and 10 years into their disease. A true incidence at 10 years cannot be ascertained because patients with no ongoing or changing symptoms do not have serial MRIs and many patients have been followed for fewer than 10 years after LP shunting. Symptoms in these 4 patients prompted MRI re-evaluation and discovery of their new cerebellar tonsilar prolapse (all 4) and cervico-cerebellar syndromes (1) (1). All had an ongoing and escalating headache and transient visual obscurations but no new visual loss. Two had neck and backaches, one with cervical radiculopathy (syrrinx), One developed sixth nerve paresis and diplopia. All 4 complained of dizziness, concern about safe footing and depth perception, inability to exercise or tolerate steps and pounding, and slower thinking and impaired concentration. One suffered syncope, a fall down a flight of steps, and subdural hematoma necessitating urgent management. Management in these 4 patients was removal of the LP shunt followed by ventriculoperitoneal (VP) shunting and optic nerve sheath decompression in the syrinx patient, additional VP shunt in 1, and suboccipital decompression in 2. All 4 improved after these procedures.

ORBITAL FRACTURES COMPLICATED BY LATE ORBITAL HEMORRHAGE AND VISION LOSS

Background: Although the nature of orbital fractures usually provides an avenue for ready orbital decompression, sequestered and clotted blood within the adjacent sinuses or subperiosteal space can limit this decompression, leading to late orbital and visual compromise.

Purpose: To present two cases of delayed retrobulbar hemorrhage and vision loss in the setting of facial trauma.

Patients/Methods: Two patients, both of whom suffered orbital floor fractures, presented with normal visual acuity that deteriorated within hours of initial exam due to retrobulbar hemorrhage. Although the orbital fractures should have permitted free drainage of orbital blood, CT showed sequestered blood within the maxillary sinuses of one patient and in the inferior subperiosteal space of the other, thus compromising orbital drainage. Both patients underwent canthotomy and cantholysis, with return of baseline vision.

Results/Conclusion: Orbital hemorrhage with visual compromise is a well known sequela of both orbital trauma and the subsequent reconstructive surgery. Visual loss in this situation is usually occurs in the acute setting. Late visual loss is unusual. Although the nature of orbital fractures usually provides an avenue for ready orbital decompression, sequestered and clotted blood within the adjacent sinuses or subperiosteal space can limit this decompression. Visually threatening hemorrhage can then occur, especially in the face of recurrent or persistent hemorrhage. This may occur hours after an initial normal exam. Clinicians must be vigilant of late visual deterioration, as prompt intervention can be sight sparing.

LATE COMPLICATIONS OF RETAINED INTRA-ORBITAL FOREIGN BODIES AND INDICATIONS FOR SURGICAL MANAGEMENT

Background: The devastating effect of ocular trauma from intra-ocular and intra-orbital projectiles has been well documented in the medical literature. While common knowledge suggests that retained intra-orbital metallic foreign bodies that are not causing any sequelae should be left in place, there are currently no clear guidelines of when removal of a symptomatic retained intra-orbital should be undertaken. We present five cases with late complications of retained intra-orbital foreign bodies, where surgical management was employed to preserve vision and provide symptomatic relief.

Objective: To present five cases with late complications from retained intra-orbital foreign bodies and discuss their surgical management.

Methods: Case series and discussion of findings.

Results: Of the five cases in this series, four presented with a retained BB at the orbital apex; one with progressive visual loss and gaze-evoked amaurosis, one with vision that progressed to CF within 24 hours of presentation, one with a late complication of severe pain with abduction, and the fourth with vision of NLP at presentation that failed to improve on steroids. All showed resolution of symptoms following surgical removal of the offending foreign body, except for the fourth case, which did not show any improvement in vision after removal. The fifth case involved incarceration of an anteriorly retained BB into the lacrimal sac, with resulting dacrocystitis that also resolved with surgical removal.
Conclusion: While non-symptomatic retained intra-orbital foreign bodies can often be left in place in order to avoid the risks of surgical removal, foreign bodies that begin to cause visual deterioration or create significant pain and disruption of surrounding structures should be considered for surgical management. The best surgical result seems to be obtained when functional vision exists prior to late complications. Surgical removal did not provide any improvement in the patient with visual acuity of NLP at presentation.

OPTIC NEUROPATHY IN CHILDREN WITH LYME DISEASE
T. R. Hodges III, A. Steere: Boston, Massachusetts

Four children with Lyme disease developed different types of optic neuropathy after contracting Lyme disease. One had bilateral papillitis with visual loss due to subretinal fluid accumulation (demonstrated by optical coherence tomography). A second child had unilateral optic neuritis six months after the initial illness. A third had papilledema associated with Lyme meningitis and a fourth child went blind from atrophic papilledema possibly combined with optic neuritis. Children with optic neuritis or papilledema may have Lyme disease and those with Lyme disease should be evaluated for optic neuropathy if they have visual complaints. Visual loss from "papillitis" may be due to subarachnoid edema as well as inflammation within the optic nerve.

VISUAL FIELD TECHNICIAN PERFORMANCE IN THE OCULAR HYPERTENSIVE TREATMENT STUDY (OHTS)

Purpose: The goal of the OHTS is to determine if topical ocular hypotensive medications prevent or delay the onset of glaucoma in ocular hypertensive patients. We examined the trends of visual field technician performance in quality control and reliability of visual fields.

Methods: Follow-up visual fields are performed every six months and are monitored for quality control and reliability. As of September 2000, 38,517 eligibility and follow-up visual fields have been performed on 1,636 patients in the OHTS. The Visual Field Reading Center examined quality control scores and reliability parameters of all the visual fields. The OHTS quality control system addresses three areas of technician quality control performance: (1) test parameter errors, (2) patient data errors, and (3) shipment errors. An average number of fields and error points were generated for both technician and year. We identified trends and performance in correlation between reliability and quality of performance with such factors as: (1) technician testing volume, (2) experience with protocol, (3) progression of abnormal fields, and (4) changes in equipment.

Results: We observed an increase in total error rate during transition of new technicians and equipment; however, the vast majority of quality control scores for each technician improved over time (experience). Of 38,486 visual fields (31 visual fields served in the visual field and nerve fiber layer measurement. Automated visual fields (Humphrey 24-2) and OCT were performed on both eyes of 16 patients with different types of optic nerve damage (raised intracranial pressure = 3, ischemic = 4, compressive = 5). Seven of these patients were also re-tested over time. The asymmetry in visual threshold and nerve fiber layer thickness between the two eyes at six regions of the visual field and the corresponding nerve fiber layer asymmetry in the same sectors were displayed on a scatter-plot.

Results: Patients that had reversible optic neuropathy clustered into a group of points on the scatter-plot that showed significant asymmetry of visual field sensitivity but little asymmetry of nerve fiber layer thickness. Patients with recovered visual function but optic atrophy clustered into a group of points which showed asymmetry of nerve fiber layer thickness but little asymmetry in visual field sensitivity. Patients with chronic optic neuropathy with visual loss and optic atrophy showed a proportional asymmetry in visual threshold and nerve fiber layer thickness. Comparisons between the structure and function of the nerve fiber layer in non-glaucomatous optic neuropathy may provide a new means of classifying damage to the visual pathway as to etiology, extent, and reversibility. Asymmetry analysis may help to overcome inter-individual variability observed in the visual field and nerve fiber layer measurement.

VETERANS ADMINISTRATION MERIT REVIEW GRANT

THE TRANSFORMATION OF PSEUDOTUMOR CEREBRI TO PSEUDOTUMOR SYNDROME: SAGITTAL SINUS MENINGIOMA NINE YEARS LATER
R. N. Santos, J. D. Wirtschafter, A. R. Harrison: Minneapolis, Minnesota

Background: Most pseudotumor cerebri (PTC) patients have a protracted course during which other disease entities may develop and their symptoms may actually masquerade as merely a continuation of the patients' already existent PTC.

Objectives: To report a case of PTC which later developed into a PTC secondary to a sagittal sinus meningioma.

Methods: Case report.

Results: In 1991, a mildly obese 25-year-old woman presented with a three-month history of headaches and bilateral decreased vision. Her CT scan was normal while a lumbar puncture revealed an increased opening pressure of 240 mm CSF. The patient was managed medically without satisfactory relief of symptoms. Within three weeks of initial neuro-ophthalmology consultation, the patient's visual acuities rapidly declined along with significant deterioration of Goldmann visual fields. Bilat-
eral optic nerve sheath fenestration was performed. The patient responded well to the procedure. During the next eight years, the patient had intermittent headaches as well as fluctuating vision especially in the right eye. The patient had normal head MRIs in 1995 and 1997 as well as a normal MRV in 1997. The patient would eventually undergo two more repeat optic nerve fenestrations in the right eye (1992 and 1995), placement of a ventriculoperitoneal shunt (1997), and a revision of the VP shunt which malfunctioned (July 2003). Prior to the VP shunt revision, a repeat head MRI showed a tumor thought to be a meningioma adjacent to and infiltrating the agittal sinus from the left posterior parietal region. The tumor could not be identified on the prior studies. The meningioma was partially obstructing venous flow and may well have contributed to the patient’s “PTC.”

Conclusion: This case illustrates the need to closely follow PTC patients not only clinically but also with repeated timely appropriate neuro-imaging techniques (MRI and/or MRV) at the point where there is even the slightest suspicion of other causes of increased intracranial pressures.

THE INTRACRANIAL TUBERCULOMA THAT WAS THOUGHT TO BE NEUROSARCOIDOSIS
R. N. Santos, E. Eggenberger, D. Kaufman; Minneapolis, Minnesota

Background: Intracranial tuberculomas and neurosarcoidosis, although both granulomatous disorders, are distinct clinical entities that are managed quite differently. As much as they are different from each other, it may be difficult to differentiate their neurologic manifestations from one another or even from other intrinsic masses of the brain. Intracranial tuberculomas are rare in developed countries thus making their underdiagnosis likely.

Objective: To describe some of the dilemmas in the diagnosis and management of a case of an intracranial tuberculoma that was initially thought to be a biopsy-proven case of neurosarcoidosis.

Methods: Case report.

Results: A 27-year-old Somalian woman with an unremarkable past medical history had a generalized toxic-clonic seizure one day after giving birth to a healthy baby girl. Neuro-ophtalmologic exam was essentially unremarkable with the exception of Goldmann visual fields which demonstrated a right superior visual field defect. At the time of her evaluation she had a 3 cm left parieto-occipital mass with edema. MRI of the brain showed a solid-appearing, irregular enhancing left mesial parieto-occipital mass with some corpus callosal mass effect. Stereotactic brain biopsy revealed non-necrotizing granulomas consistent with neurosarcoidosis. AFB culture of the tissue sample was negative. The patient was treated with Prednisone and was eventually lost to follow-up.

Two months later, the patient had another seizure and she was re-hospitalized with Frisian grade 5 disc edema OU (OD>OS). Repeat MRI of the brain revealed a new 1 cm left occipital extension of the previously noted mass within the calvarium. A brain biopsy via a craniotomy done showed caseating granulomatous inflammation, consistent with a tuberculoma. There were few suspected non-viable mycobacteria organisms identified by special stain. There was no evidence of malignancy. The patient was then treated accordingly with isoniazid, pyrazinamide, rifampicin, ethambutol, pyridoxine, prednisone, and phenytoin.

Conclusion: As much as a brain biopsy would most of the time validate the diagnosis of an intracranial tuberculoma, it would not be unwise to try a 6-8 week therapeutic trial with anti-TB drugs with regular monitoring of the patients with CT or MRI scans where facilities are limited and when a brain biopsy may be contraindicated. Surgical excision is usually reserved for cases that result in increased intracranial pressure secondary to the lesion that is not responsive to medical therapy. Occasionally, new intracranial tuberculomas or expansion of the existing lesions may occur despite anti-TB therapy. In such cases an adjuvant therapy of steroids (e.g. dexamethasone, prednisone) for 4-8 weeks may be effective.

BILATERAL OPTIC NEUROPATHY SECONDARY TO MANGANESE TOXICITY
J. R. Lewis; Edmonton, Alberta

Background: Manganese is a common heavy metal, occupational exposure to which may occur via skin absorption or inhalation of fumes in the pottery and electroplating industries. A syndrome of chronic manganism has been described in the occupational medicine literature, with neurological symptoms including Parkinson-like tremor, fatigue, tinnitus, memory loss and vague visual disturbances. No documentation of visual loss could be found in the ophthalmological literature.

Objective: To describe a case of severe central visual loss in a man with manganese toxicity.

Methods: Observational case report and literature search.

Results: A 50-year-old male machinist working in an electroplating laboratory developed blurred vision and polypodyia first in his right eye, and a few weeks later in his left eye. The blurred vision persisted, and he subsequently developed headaches, memory loss, leg pain, fatigue, weight loss and a constant resting tremor of his right hand. These features were felt to be clinically consistent with manganese toxicity, and serum manganese was elevated. Visual acuity was 20/300 in each eye, despite a structurally normal neuro-ophthalmological examination. Goldmann visual fields demonstrated bilateral centro-cocentral scotomas. CT scan and MRI of brain and orbits were normal. ESR was normal, and temporal artery biopsy was negative. Electroretinogram was normal. Visual evoked response on two occasions demonstrated significantly prolonged latency bilaterally.

Conclusion: Manganese has not previously been reported to be significantly toxic to the visual pathways. A case is presented that demonstrates severe bilateral central visual loss in a machinist with neurological manifestations consistent with manganese poisoning and no other apparent cause for the visual loss.

PHOTOSENSITIVITY AS THE PRESENTING SYMPTOM OF CHIASMAL COMPRESSION
A. Kawasaki, V. Purvin; Indianapolis, Indiana

Background: Compressive optic neuropathies typically produce dimming and loss of vision. We describe five patients with a chief visual complaint of photosensitivity and/or glare who were subsequently found to have a compressive lesion of the optic chiasm.

Objective: To describe an unusual symptom of chiasmal compression.

Methods: Five case histories.

Results: Five patients between ages 19 and 43 years were identified. The primary symptom in each patient was an increased sensitivity to light, described as things "looking too bright" or "glarey". The duration of the photosensitivity from
onset to diagnosis ranged from 1 week to 1 year. The only other visual symptom was mild blur of one eye in one patient. An additional patient developed blur in one eye 9 months after onset of photosensitivity. Four patients had associated headache. Examination showed no loss of visual acuity in 7 of 10 eyes, one line drop in one eye, two lines in one eye and three lines in one eye. Visual field testing was normal in one patient. In two patients, there was a bitemporal visual field deficit (mild in one and marked in the other but not respecting the vertical meridian) and in one patient, there was mild central defects. The fifth patient had extensive pre-existing field losses from choroidal scarring.

MRI scanning revealed a suprasellar mass in all patients (pituitary adenoma in three patients, chordoma in one patient and craniopharyngioma in one patient).

Conclusion: Although photosensitivity is usually considered to have an ocular origin, we have encountered five patients in whom this symptom was the presenting manifestation of an intracranial lesion, specifically a suprasellar mass.

THREE DIMENSIONAL ANALYSIS OF SACCADE ABNORMALITIES IN UNILATERAL SIXTH NERVE PALSY

A. M. F. Wong, D. Tweed, J. A. Sharpe; Toronto, Ontario

Background: The effects of unilateral sixth nerve palsy on dynamic properties of saccades have not been systematically investigated.

Objective: To analyze saccade performance in patients with unilateral sixth nerve palsy.

Methods: Twenty-seven patients with unilateral sixth nerve palsy (7 severe, 11 moderate, 9 mild) and 10 normal subjects were studied. Eye movement recordings were performed using magnetic sleral search coils in each eye during monocular viewing. Saccades amplitude and peak velocity were calculated for horizontal, vertical and torsional (quick phase) saccades.

Results: In patients with severe palsy, during paretic eye viewing, the paretic eye made a series of hypometric horizontal saccades in the direction of the paretic gaze until the final eye position reached was close to the target. At the same time, the normal occluded eye made a series of saccades of decreasing amplitude, and reached a final eye position that overshot the target (secondary deviation). During normal eye viewing, the paretic eye made a hypometric saccade in the direction of the paretic gaze with the final eye position undershooting the target, while the normal eye made a normometric saccade and reached a final eye position that matched the target position (primary deviation). The peak velocity of horizontal saccades were subnormal in both eyes in both directions under both viewing conditions (p < 0.001). In contrast, in moderate and mild palsy, horizontal saccade amplitude was normal, but peak velocity was subnormal in both eyes in both directions under both viewing conditions (p < 0.001). Vertical saccades and torsional quick phases were normal in all three groups of patients.

Conclusions: In severe palsy, during paretic eye viewing, the normal eye made a series of saccades in the direction of the paretic gaze, the amplitude of which correlated with the difference in target position and actual position of the paretic eye. This suggests that Hering's law is obeyed, with retinal error signal from the paretic eye driving both eyes. Saccade velocity was decreased in both abduction and adduction in the paretic eye, suggesting that elasticity and/or viscosity of the plant were altered. Adaptation to changes in the paretic eye may explain the decreased saccade velocity in the normal eye.

Grant: E. A. Baker Foundation (Canadian National Institute).
Results: Cell viability was markedly reduced by 10 min exposure to 1 mM glutamate followed by 1 hr incubation in glutamate-free medium. Simultaneous application of diazoxide at concentrations of 0.1-10 μM with glutamate exhibited dose-dependent protection against glutamate neurotoxicity. The protective action of diazoxide (10 μM) was inhibited by simultaneous application of 5-ITE (10 μM). One min after exposure to 1 mM glutamate, most of the retinal neurons showed mitochondrial membrane depolarization, which was inhibited by simultaneous application of diazoxide (10 μM).

Conclusions: These results suggest that opening of mKATP channel protects retinal neurons against glutamate neurotoxicity by inhibiting the glutamate-induced mitochondrial membrane depolarization that leads to neuronal death.

Grant in aid for scientific research from the Ministry of Education, Science and Culture, Japan.

HYDROCEPHALUS SECONDARY TO ISOLATED SPINAL CYSTICERCOSIS
M. B. Strominger, D. L. Carter-Meeman, R. N. Hargreave; Brooklyn, New York

Background: Hydrocephalus is a common complication of Neurocysticercosis and is usually due to obstruction by cisternal or ventricular cysts, or subarachnoid spaces by diffuse basilar meningitis. Spinal cysticercosis is an uncommon manifestation seen in 0.7 to 6% of cases. It is thought to be due to downward migration of larvae from the cerebral to the spinal subarachnoid spaces with possible ventriculoperitoneal infiltration or hematoencephalitis. We report the unusual case of isolated spinal involvement leading to hydrocephalus.

Case Report: A 35-year-old Mexican gentleman presented with chronic headaches for six months. Visual acuity was 20/20 OU with normal color vision. Dilated fundus examination showed both optic nerves to be swollen without significant hemorrhage or edema. MRI revealed enlargement of the lateral and third ventricles consistent with hydrocephalus. No intraventricular or intraparenchymal lesions were seen. CSF revealed 87 WBC's (85% lymphocytes, 6% monocytes, and 6% eosinophils). Protein was 100 mg/dl and glucose 37 mg/dl. MRI of the spine revealed an intraspinal increased intensity focus at thoracic level T10/11. Neurosurgical biopsy of the intraspinal mass revealed multiple intradural and epidural cystic masses consistent with cysticercosis. The patient was started on Albendazole 400mg bid and Decadron 10mg q6h with resolution of his headaches and papilledema.

Conclusion: Neurocysticercosis usually presents with cysts associated with cysts within the ventricular system or brain parenchyma. Our case is unusual in that the Cysticercus cysts were isolated to the spinal column.

Grant: SUNY Downstate Medical Center

EXTREMELY HIGH RESOLUTION MRI OF THE HUMAN OPTIC NERVE REVEALS LHON ASSOCIATED PATHOLOGY
A. A. Sadun, V. Corelli, S. Bose, E. T. Ahrens; Los Angeles, California

Magnetic Resonance Imaging (MRI) is a potent tool in both the clinical and research realms as it is non-invasive and allows views into optically opaque specimens. Extremely high-resolution MRI (MR microscopy-MRN) is an emergent technique which provides three-dimensional views in intact living animals or excised tissue. The high-resolution in combination with the availability to view the tissue in any plane allows this method to complement established morphological approaches.

We examined the optic nerves from two normal controls (69-year-old man and 70-year-old woman) and one 73-year-old woman with Leber's Hereditary Optic Neuropathy (LHON-3460). In each case an 8 mm diameter ring of peripapillary retina choroid and sclera together with about 6-8 mm of optic nerve were dissected free and deep fixed in mixed aldehydes. The specimens were then rinsed and emersed in perfluoropolyether and sealed into a 10 mm diameter quartz tube. Imaging was performed on a 15 Tesla Bruker MRI with an Acuscan shielded gradient coil. Data was acquired from a conventional three-dimensional Fourier transform spin-echo imaging protocol that yielded a final isotropic resolution of 30 μm. Sagittal axial and coronal sections through all three optic nerves provided far more detail and histoarchitecture than everbefore demonstrated on MRI. The ophtalmic artery and vein could be seen as well as the individual plates of the lamina cribrosa. The Circle of Zinn-Haller could be seen in various planes. Even the retinal layers were discernable. The MRN of the LHON case demonstrated marked atrophy, wide fibrous septa and deep folds of the arachnoid and dura.

These dramatic results demonstrate the feasibility of obtaining extremely high resolution (30 μm) 3-D images of the human optic nerve by this novel technology. Several specific features, such as the collapse of the lamina cribrosa in the LHON case would be very difficult to demonstrate with standard histological preparations but most easily appreciated by rotation of the MRN imaged plane. We expect this new methodology to be useful by providing three-dimensional and microscopic characterization of optic neuropathies.

OPHTHALMOPLEGIA AND FAMILIAL FACIAL PALSY
A. G. Lee, P. W. Brazis, E. Eggenberger; Iowa City, Iowa

Objective: To alert clinicians to unusual neuro-ophthalmic presentations of patients with recurrent or familial facial palsy.

Design: Retrospective case series.

Setting: Tertiary care referral ophthalmology centers.

Participants: Three patients with familial facial palsy and ophthalmoplegia.

Results: Presentation of cases and review of literature.

Conclusion: Clinicians should be aware that ophthalmoplegia and familial cases can occur in facial palsy.

ORBITAL APEX COMPLICATIONS OF NEUROSURGERY
A. G. Lee, R. Tang, J. Schiffman; Iowa City, Iowa

Purpose: To report orbital complications of Neurosurgery.

Method: Retrospective case series.

Setting: Tertiary care neuro-ophthalmology referral center.

Results: Case one: right orbital apex syndrome with loss of vision and a third nerve palsy in the right eye after attempted transphenoidal surgery. Case two: Orbital apex syndrome due to presumed orbital compression during face-down lumbar spine surgery.

Conclusions: Although rare, clinicians should be aware of the potential for orbital apex syndrome during neurosurgical procedures.

ORBITAL PRESENTATIONS OF GIANT CELL ARTERITIS
A. G. Lee, R. A. Tang, S. E. Feldon, M. Pless, J. S. Schiffman, R. M. Rubin, N. Rao; Iowa City, Iowa

Background: To alert clinicians to the orbital presentations of giant cell arteritis.

Design: Retrospective case series.

Setting: Tertiary care referral ophthalmology centers.

Participants: Four patients with orbital manifestations of giant cell arteritis.

Results: Presentation of cases and review of literature.

Conclusion: Clinicians should be aware that giant cell arteritis may have orbital manifestations.

IMPROVEMENT IN PAPILLEDEMA AND VISUAL LOSS AFTER ENDOVASCULAR STENT PLACEMENT IN DURAL SINUS THROMBOSIS
M. G. Hunt, A. Lee, R. Kardon, J. Chaloupka; Iowa City, Iowa

Objective: To report two cases of cerebral venous sinus thrombosis with papilledema and visual loss that improved after endovascular stent placement.

Materials and Methods: Retrospective case series from a tertiary ophthalmic center.

Results: Two cases of venous sinus occlusion treated with angioplasty and stenting are described. Both cases experienced improvement in optic disc edema and visual function following the procedures.

Conclusion: Endovascular stent placement may relieve increased intracranial pressure and papilledema caused by cerebral sinus thrombosis and may prevent further visual loss.

ANTERIOR ISCHEMIC OPTIC NEUROPATHY ASSOCIATION WITH CATARACT EXTRACTION: TIME OF OCCURRENCE AND RISK FACTORS
T. J. McCulley, B. L. Lam, W. J. Feuer; Kettering, Ohio

Background: The existence and nature of a causal relationship between cataract extraction (CE) and non-arteritic anterior ischemic optic neuropathy (NAION) have been debated.

Objective: To evaluate the association between CE and NAION by 1) analysis of time of NAION occurrence after CE and 2) comparison of prevalence of risk factors between patients with CE-associated NAION and patients with spontaneous NAION.

Methods: First, the records of all patients diagnosed with NAION and cataract at Bascom Palmer Eye Institute from 1993 to 2000 were reviewed for occurrence of NAION within one year after CE by phacoemulsification or phacofracture. Next, using the Fisher's exact test, the prevalence of NAION risk factors were compared between patients with NAION following CE and patients with spontaneous NAION during the study period.

Results: All 17 cases of NAION occurring within 1 year after CE occurred within 6 months after CE with none occurring during the second 6-month period (p < 0.001, binomial distribution). When these 17 CE-associated NAION cases were compared with the 37 spontaneous NAION cases found during the study period, the prevalence of diabetes mellitus, hypercholesterolemia, and tobacco use were similar, but the following risk factors were notably lower in the CE-associated NAION group: HTN (29% vs. 68%, p = 0.017), the proportion of patients with a C:D ≤ 0.2 in the involved eye (60% vs. 94%, p = 0.007) and, the proportion of patients with a C:D ≤ 0.2 in the contralateral eye, (63% vs. 89%, p = 0.052).

Conclusion: The time distribution of NAION after CE strongly suggests a causal relationship between CE and occurrence of NAION. Patients with NAION following CE have a lower prevalence of hypertension and tend to have larger cup-to-disc ratio than those with spontaneous NAION.

VISUAL FIELD SCREENING: PROSPECTIVE, MASKED TRIAL WITH A COMMERCIAL LASER POINTER
M. S. Lee, M. J. Volpe, S. L. Galetta, G. T. Liu, M. G. Maguire, L. J. Balcer; Philadelphia, Pennsylvania

Background: Visual field screening identifies patients requiring further diagnostic testing and formal visual fields. Conventional confrontation techniques are quick and simple to perform, but may miss subtle defects.

Objective: To compare the sensitivity of another technique, laser pointer visual fields (LVF), with confrontation visual fields (CVF) for identifying eyes with abnormal Humphrey visual fields (HVF).

Methods: Patients presenting for HVF prospectively underwent CVF and LVF testing in an outpatient exam room setting. The examiner was masked to diagnoses of known field defects. LVF was performed using a commercial laser pointer projected onto a tangent screen. Points were tested along the horizontal and vertical meridians, around the blindspot, and in each quadrant. LVF subjectively assessed central field and then single and double simultaneous finger counting in all quadrants. LVF and CVF were considered abnormal for any defect. HVF was regarded as abnormal if the mean deviation (MD) < -3.00. Sensitivity and specificity were calculated to account for inter-eye correlation.

Results: 90 patients underwent testing (175 eyes). 25 eyes were excluded for unreliable HVF parameters. There were 80 normal and 70 abnormal HVF. The LVF and CVF had an overall sensitivity of 71% and 26% and a specificity of 89% and 99% respectively (p < 0.0001). The average testing time per eye was 0.5 min for CVF, 1.5 min for LVF, and 8.0 min for HVF. A subset analysis of more severe HVF defects (MD < -6.00) increased sensitivity to 90% and 40% for LVF and CVF respectively.

Conclusions: LVF testing is significantly more sensitive than confrontation techniques to screen visual fields. While HVF should be performed when possible in patients with suspected defects, LVF testing represents an effective and time efficient tool for bedside and office visual field screening in patients with suspected afferent visual pathway disease.

WILD CAT SCRATCH DISEASE
M. A. Lana-Perixoto, L. Osvaldo, M. Cabral, I. R. Souza; Belo Horizonte, Brazil

Background: Cat scratch disease is a common cause of fever, malaise and lymphadenitis. Neuro-retinitis occurs in less than 1.5 % of these patients and is usually characterized by loss of vision, optic disc edema and exudates in the retina forming a macular star.

Objective: To report a case of cat scratch disease transmitted by a wild cat. To demonstrate that wild cats and not only domestic cats and fleas can transmit the disease.

Case Report: A 34-year-old man, Captain of the Brazilian Army in service in the Amazonian forest noticed severe pain in his right eye followed by sudden loss of vision. He had presented with low-grade fever, malaise and cervical lymphadenitis two weeks earlier. He reported he had been scratched by a wild cat few weeks before the onset of the symptoms. The
examination showed visual acuity RE 20/400; LE 20/20; he could read no Ishihara plate with the RE and 6 of 8 with the LE. Fundus examination disclosed bilateral optic disk edema (more severe in the RE) and the presence of retinal exudates forming a macular star bilaterally. There was also an afferent pupillary defect in the RE. A brain MRI was normal and a CSF examination revealed opening pressure of 12 cm H20, 6 cells/mm² (neutrophils 15%), glucose 73%, protein 35 mg% and a gamma-globulin concentration of 9.5%. ELISA for Bartonella henselae was positive in the serum and CSF. The patient was given IV methylprednisolone and ciprofloxacin. Two months later his visual acuity was RE 20/40, LE 20/20, there was complete recovery of the optic disk edema but only slight absorption of the macular star in both eyes.

**Conclusion:** To the best of our knowledge this is the first report of cat scratch disease transmitted through scratches by a wild cat.

**OPTIC NEUROMYELITIS IN SCHISTOSOMIASIS MANSONI**

M. A. Lana-Peixoto, L. O. Cabral, A. Muniz; Belo Horizonte, Brazil

**Background:** The cause of optic neuromyelitis (Devic's Syndrome) is unknown. A few reports have described Devic's syndrome in association with systemic lupus erythematus, tuberculosis and AIDS.

**Objective:** To describe a case of optic neuromyelitis secondary to schistosomiasis mansoni.

**Case Report:** A 34-year-old man developed sudden loss of the temporal field of vision of both eyes three days following the onset of severe headache. In the next few days he could only see hand movements with both eyes. A brain MRI showed a T2-hyperintense and gadolinium-enhanced lesion in the sellar and suprasellar areas, extending to the intracranial portion of both optic nerves and thickening of the optic chiasm and optic tract. A biopsy of the lesion showed the presence of inflammatory cells and reactive glial tissue. The patient was treated with corticosteroids with good recovery. Fourteen months later he developed severe pain at T10 level, dysesthesia caudal to this level and marked paraparesis with urinary sphincter dysfunction. A spinal cord MRI revealed a T2-hyperintense lesion in the sellar and lumbar levels. Cerebrospinal fluid examination disclosed 35 cells/mm² (33% eosinophils); proteins 60 mg%; glucose 55 mg% and a positive indirect immunofluorescence reaction to schistosoma mansoni. The patient was treated with IV methylprednisolone followed by oral prednisone. At follow-up he presents VA RE 20/25, LE 20/30, a slight pallor of the temporal aspect of the optic discs and normal visual fields. Motor examination is normal but there are decreased light touch sensation below T10 and decreased vibration sense in the knees and malleoli.

**Conclusion:** Neuroradiologists optica is usually considered a form of acute disseminated encephalomyelitis. To the best of our knowledge this is the first case of optic neuromyelitis in association with schistosomiasis mansoni reported in the world literature.

**THE SHAPE DISTORTION EFFECT IN CEREBRAL DYSCHROMATOPSIA AND PROSOPAGNOSIA**

J. S. Kim, J. Rivest, J. Intrilligator, J. A. Sharpe, Cheju, Cheju, Korea

**Background:** Form perception, face recognition, and color perception are processed by the parvocellular visual pathway in the ventral stream of the occipital and temporal lobes. When two shapes are presented successively and briefly to normal subjects, the perceived form of the second (test) shape is changed dissimilar to the form of the first (priming) shape. This shape distortion effect has been postulated to originate from adaptation of non-retinotopic and non-feature-specific neurons in the ventral stream.

**Objective:** To determine differential effects of cerebral lesions on the perception of face and color, and on higher cortical processing of shape interaction.

**Methods:** We measured the shape distortion effect in two patients, one with cerebral dyschromatopsia and the other with cerebral dyschromatopsia and prosopagnosia from bilateral occipitotemporal infarcts. For each trial, flashed in succession were a priming rectangle (45 ms; vertically or horizontally), a gap of 180 ms, a test circle (60 ms), and a random-dot mask (300 ms). The priming rectangle and the test circle were flashed in each quadrant with an eccentricity of 8.6 degrees from the fixation point that located in the center of the monitor. After each trial, using the method of adjustment, the % elongation ([longer diameter] - [shorter diameter])/[shorter diameter] X 100 of the reproduced circle or ellipse was computed.

**Results:** The two patients demonstrated normal perception of shape distortion, and normal evaluation of shapes in general. Conclusions: Impaired recognition of faces or perception of colors can be dissociated from shape perception. Normal perception of the shape distortion in the presence of cerebral achromatopsia and prosopagnosia provides evidence for cortical segregation of specialized visual areas in the ventral stream for recognition of faces and colors and for processing of shape interactions.

**ASYMMETRIC PAPILLEDEMA IN IDIOPATHIC INTRACRANIAL HYPERTENSION: AN INSIGHT**

E. R. Eggenberger, A. Pathak, N. P. Desai; East Lansing, Michigan

**Background:** Papilledema may be asymmetric or unilateral. Proposed mechanisms have included asymmetric intracranial pressure and anatomical variations in the optic nerve sheaths, such as adhesions or leaks that prevent transmission of intracranial pressure along one nerve.

**Objective:** To gain insight into the mechanism of unilateral papilledema.

**Method:** We report a case of a 33-year-old, healthy female presenting with a three week history of transient visual obscurations OD. Examination was notable for weight of 180 pounds on a 5'1" frame. Visual acuity was 20/15 OU, while color vision was 10/10 HRR plates OU, and there was no evidence of RAPD. Goldmann perimetry revealed an enlarged blind spot OD. Fundus examination revealed disc edema OD with fine splinter hemorrhages (Frisiu Grade 4), and an unremarkable appearing disc OS.

**Results:** Orbital T-2 coronal MR imaging demonstrated increased CSF fluid symmetrically along both optic nerve sheaths. Specifically, no adhesions or restrictions to CSF flow were noted along the left optic nerve sheath. A lumen puncture revealed an opening pressure of 240 mm H2O with normal composition and cytology. A diagnosis of idiopathic intracranial hypertension (IHH) was made and the therapy was initiated with acetazolamide 1000 mg qd. Follow-up examinations two and six months later demonstrated resolution of disc edema OD.

**Conclusions:** The factors contributing to the occurrence of unilateral papilledema in IHH probably act at the level of the lamina cribrosa, and have yet to be fully elucidated. Possibilities include differences in the scleral canal, nerve head vascular supply or glial supporting structures.
TWO UNUSUAL CASES OF PROLACTINOMA
D. Lin, A. Benton, R. L. Sogg; Stanford, California

Two males, one age 17, the other 36, presented with unusual manifestations of prolactin-secreting pituitary tumor. The first has a history of hypoparathyroidism with renal calculi. This past summer he had noticed an inability to follow a passed football when directly overhead but not before or after it arrived and left. No change in libido or impotency noted, nor galactorrhea. Prolactin was 470 ng/ml. Almost complete bilateral hemianopia with large bitemporal pituitary adenoma. After a single pill of cabergoline (.5 mg BIW) VF almost returned to normal and prolactin to 40. 2 mos after therapy VF normal, but tumor showed NO REGRESSION on MRI.

Second case concerns a 36 year old man with long history of depression, left hemiparesis, left homonymous hemianopia, galactorrhea, and prolactin greater than 10,000 ng/ml. Huge pituitary adenoma invading both cerebral hemispheres, initially treated by cabergoline with only TRANSIENT LOWERING of prolactin, then followed by subtotal removal of tumor, with a fading response to cabergoline after craniotomy. Interesting MRI scans will be shown.

A CASE OF ORBITAL METASTASIS FROM GASTRIC CARCINOMA
E. Z. Karam, D. Savino, M. Ramella; Caracas, Venezuela

Background: Metastases from gastric carcinoma are unusual in the orbit and comprise a 1% of all orbital metastases. The common metastatic sites of these tumors are liver, lung, peritoneum, bone, adrenal glands and rarely central nervous system. We report a case of orbital infiltration from a gastric adenocarcinoma. Objective: To present a case of metastatic gastric carcinoma to the orbit. Methods: Case report. A 70-year-old man developed progressive lid swelling, diplopia, painless ophthalmoplegia and proptosis in the left eye. After 4 weeks, he began to lose vision in the left eye. His past medical history was remarkable for a palliative resection of a grade IIIa gastric adenocarcinoma with infiltration of regional lymph nodes two years before. He underwent radiotherapy and chemotherapy at that time. Ophthalmic examination showed best-corrected visual acuity of 20/30 in the right eye and hand movement in the left eye. The right eye was normal. His left eye had a relative afferent pupilary defect. Ocular mobility was restricted in all positions gaze with 12 PD exotropia in primary gaze. Forced duction test was positive. He had a 10 mm proptosis. His intraocular pressure was elevated (35 mmHg). Slit-lamp examination demonstrated chemosis and corneal ulcer from exposure keratitis. The eye fundus exam was normal. CT and MRI revealed enhancement of the orbital muscles with “honey pattern” in the orbital fat and optic nerve compression. Results: Orbital biopsy demonstrated infiltration by gastric adenocarcinoma. Radiation therapy to the eye was initiated. Conclusions: The major clinical features of orbital metastases are the relatively rapid progression of painless ophthalmoplegia, proptosis and visual loss. The clinical and neuroradiological findings may mimic orbital inflammation, Tolosa Hunt syndrome, thyroid ophthalmopathy or cellulitis. Orbital metastases should be included in the differential diagnosis in all patients with idiopathic orbital inflammation, especially those with a past history of cancer.

MALIGNANT GLIOMA OF THE OPTIC PATHWAYS IN ADULTHOOD
E. Z. Karam, R. Muci-Mendoza, M. Ramella; Caracas, Venezuela

Background: Malignant gliomas of the optic pathways are quite uncommon. These tumors usually cause rapid visual loss. Early clinical and neuroradiological diagnosis is almost always elusive. Objective: To describe the clinical and pathological findings of malignant optic gliomas in two patients. Methods: Case reports. A 69-year-old man developed painful visual loss in the left eye (OS). Neuroophthalmologic examination demonstrated no light perception, an amaurotic pupil, partial ophthalmoplegia, and an ischemic optic neuropathy OS. The right eye (OD) had a visual acuity of 20/15 with a normal ophthalmologic examination. After one week, the patient developed central retinal vein occlusion OS. One month later he experienced visual loss OD. Best-corrected visual acuity was 20/40 with no abnormal findings. He was put on steroids and vision improved to 20/25 in four weeks. Two months later, he woke up with a painful and swollen OS. Central retinal artery occlusion and myelitis extension was observed in the optic nerve head. A 70-year-old man developed rapidly progressive painless visual loss in both eyes, more pronounced in OS. Visual fields exhibited bitemporal hemianopia. The rest of his ophthalmologic examination was normal. In both cases MRI showed a mass lesion with gadolinium enhancement of the optic nerves and tracts. Results: Brain tissue biopsy disclosed gemistocytic and fibrillary astrocytomas respectively and radiation therapy was begun. Conclusions: The clinical course of malignant optic gliomas is variable and depends on their origin in the anterior visual pathways. The first case exhibited the classical pattern of infiltration of the distal portion of the optic nerve as described previously by Hoyt and coworkers. The second case evidenced the intracranial origin pattern with simultaneous, progressive visual loss and normal eye fundi. The diagnosis of malignant optic gliomas should be considered in adult patients with painless or painful, unilateral or bilateral, subacute visual loss.

CHLOROQUINE RETINOPATHY
J. A. Leavitt; Rochester, Minnesota

Objective: Case report. Methods: Chart review. Results: 29-year-old woman with a history of systemic lupus. She complained of difficulty with night driving in late 1999. In January 2000, she could not see the highlighting on reading material and had difficulty with her side vision while driving. Past medical history is significant for SLE diagnosed in 1989. Cervical myelitis in 1990, Bell's palsy in 1993. Examination in July 2000: visual acuity of 20/80 and 3/200, or big E at 3 feet. Relative afferent pupil defect on the left. Ishihara color plates 0/13 OU. VII nerve palsy on the left. Sharp flat discs with +1 pallor OU, marked thinning of vessels especially nasally, retinal pigment epithelial irregularity. VF: Bitemporal hemianopsia and superior binaural defects. FA: Extremely attenuated retinal vessels, rarefied RPE throughout the posterior pole in a ring-like distribution and involving the papillomacular bundle. Window defects associated with the depigmentation. Conclusions: She had been placed on 500 mg/day of chloroquine in 12/91 for a total of at least 1460 gm. This was chloroquine retinopathy.
A UNIQUE OCULAR MOTOR DISORDER CHARACTERIZING ALTERNATING HEMIPLEGIA OF CHILDHOOD
R. A. Egan, Portland, Oregon

Background: Alternating Hemiplegia of Childhood (AHC) is characterized by repeated episodes of hemiparesis or hemiplegia that alternates from side to side with subsequent attacks. The disease usually presents early in the first year of life and is frequently associated with poor outcome. Many reports have described “monocular nystagmus,” but none have realized a unique nature of this finding. This entity is unknown in the neuro-ophthalmic literature.

Objective: To characterize a unique ocular motor disorder found only in AHC and raise neuro-ophthalmologists’ awareness of this abnormality.

Methods: Case report and review of the scientific literature.

Results: A 14-month-old boy developed spells of monocular abduction at seven days of age. Abduction occurred at roughly one Hz and the fellow eye remained in primary position if not slightly deviated in an abducted direction. Each subsequent spell affected the other eye. Hemiplegia developed at seven months of age and always ipsilateral to the abducting eye. Spells were aborted with sleep, but otherwise would last minutes to hours. Consciousness was unaffected during the spells and inter-ictal neuro-ophthalmologic exam was completely normal. General neurologic exam revealed no speech output and mild generalized hypotonia. During review of videotaped spells, the patient had brief three to five second bursts of opcoscolium. Brain, chest, and abdomen imaging as well as cerebral spinal examination and biochemical work-up were completely normal. Inter-ictal EEG-CCTV was unrevealing.

Conclusions: This patient met all the requirements of the diagnosis of AHC spells of abducting “nystagmus” are a unique ocular motor finding in patients with this disorder. Ocular motility dysfunction remains elusive, but may involve a subcortical or midbrain generator with spreading depression of surrounding neural tissue.

NATURAL HISTORY OF OPTIC NERVE SHEATH MENINGIOMAS
R. A. Egan, S. Lessell; Portland, Oregon

Background: Treatment of optic nerve sheath meningiomas (ONSM) remains controversial. Options include surgical excision, stereotactic radiation therapy, or conservative management. Difficulty in decision making is made troublesome since the natural history of this disease remains unclear and double-blinded, placebo controlled treatment trials are lacking in the scientific literature.

Objective: To present the outcomes of a series of patients suffering from ONSM who were treated conservatively.

Methods: Forty-two patients were identified in our database that had ONSM. Twenty-five had been referred for visual evaluation after treatment decisions had already been made and were thus excluded from the series. The remaining 17 patients were followed conservatively.

Results: Seventeen patients were followed for a mean of 6 years (2–18 years). Nine optic nerve sheath meningiomas affected the right eye and 12 patients were female. Mean age of onset was 45.4 years (5-88) and age at diagnosis was 49.5 years (11–74). At diagnosis, 10/17 patients had >20/30 acuity and 11/17 had >20/100 acuity. At last follow-up, 5/17 had acuity >20/30 and 8/17 had acuity > 20/160. No patient suffered from a metastatic lesion from his or her optic nerve sheath meningioma and there was no increased mortality. Three patients had minimal improvement in visual acuity over a follow-up period of 6 to 8 years.

Conclusions: This series of patients confirms that most patients suffering from ONSM develop slowly progressive visual loss. A few patients may actually have mild visual improvement. Morbidity and mortality is also not increased which corresponds with the current literature. Since surgical excision may lead to near instantaneous blindness and the long-term effects of radiation therapy may include radiation optic neuropathy and development of carcinoma, conservative management offers an attractive and logical alternative.

PSEUDO-EMBOLI IN SUSAC SYNDROME

Background: Susac syndrome is a rare condition of unknown etiology characterized by microangiopathy of the retina, brain, and cochlea. Emboli have never been described in the retina of Susac syndrome.

Objective: To raise awareness of pseudo-emboli in Susac syndrome.

Methods: Case report.

Results: Four months prior to presentation, a 27-year-old man awoke with acute loss of central vision OS. At presentation he had abrupt vision loss inferiorly OD with acute onset tinnitus. He had altitudinal visual field defects OU and an occluded sheathed arteriole OD. Two bright orange refractile "emboli" were present in retinal arterioles, but not at bifurcations. A complete cerebrovascular disease evaluation was unrevealing including magnetic resonance imaging (MRI) of the brain. Several months later he developed cognitive complaints followed by central visual loss OS, aphasia and a right hemiparesis. Funduscopy revealed the sheathed occluded vessel OD and retinal edema in the macula OS. There were three new pseudo-emboli OS and one OD; none were located at a retinal bifurcation. Angiometry confirmed sensorineural hearing loss bilaterally. MRI of the brain now revealed multiple high signals scattered throughout the periventricular white matter including the corpus callosum. Two other cases of Susac syndrome with pseudo-emboli have been seen by at least two of the authors.

Conclusion: This is the first known description of pseudo-emboli occurring in Susac syndrome. Focal atheromata, or pseudo-emboli, in the retinal arteries can simulate retinal arteriole emboli. While systemic atheromatosis is a common disorder, it rarely affects the retinal vessels beyond the central retinal artery. Retinal pseudo-emboli occur in a number of other inflammatory and infectious diseases causing focal retinal arteriole wall damage allowing normal plasma lipids to leak into the arteriole wall. Their appearance is similar to Hollenhorst plaques but usually do not occur at bifurcations of arterioles. We refer to these pseudo-emboli as “Gass Plaques.”

UNILATERAL PAPILLEDEMA CAUSED BY A FRONTO-TEMPO-PAIRITETAL ARACHNOID CYST
H. E. Killer; Aarau, Switzerland

Purpose: To report a case of unilateral papilledema caused by an arachnoid cyst.

Methods: Case report. A 36-year-old woman was admitted to the ophthalmology service because of unilateral papilledema in the left eye. The patient complained of intermittent left sided headache and of pain in the left orbit of two months duration. Visual acuity measured 20/20 in both eyes without correction.
The right optic nerve head was normal. The left optic disc showed blurring of the margins and was slightly prominent. The pupils were of equal size and no relative afferent defect was present. Color vision testing with Ishihara plates was normal, 15/15 OU. There was a slight desaturation of brightness in the left eye. Ocular motility was full in all directions of gaze and a neurological examination was normal except for the papilledema OS.

A MRI was performed and demonstrated a large fronto-temporo-parietal arachnoid cyst in the left hemisacrum. In the T2 weighted image the subarachnoid space of the left optic nerve (ON) was distended due to increased cerebrospinal fluid (CSF). There was marked widening of the bulbar portion of the optic nerve, adjacent to the posterior sclera. A cystoperitoneal shunt (Sophy medium) was placed and the papilledema gradually resolved.

Conclusion: Papilledema is caused by increased intracranial pressure, usually due to an intracranial mass lesion or pseudotumor cerebri. In most cases, papilledema is bilateral, although asymmetry or even unilateral papilledema may occur. This patient presented with unilateral papilledema in the left eye due to a fronto-temporo-parietal arachnoid cyst that was in contiguity with the left subarachnoid space of the left optic nerve, causing papilledema OS. The fact that there was no papilledema in the right eye suggests that there was no communication between the left and right subarachnoid space via the chiasmal cistern.

In the normal population, a free communication between these CSF compartments is presumed in order to explain the constant pressure in all CSF compartments.

WHEN THE WORLD IS TURNED UPSIDE DOWN AND THE TELEVISION KEEPS FALLING TO THE GROUND WHILE DWARFS ARE PARADING ON THE CEILING: A COMPLEX CASE OF VISUAL HALLUCINATIONS
H. E. Keller: Aarau, Switzerland

Purpose: To report a case of a patient with a complex combination of real and pseudo hallucinations.

Method: Case report a patient with cardiac arrhythmia treated with digoxin reported blurring of vision and complained of unicolored yellowish points and stripes throughout the visual field. Ophthalmological examination was normal and a side effect of the digoxin was suspected. Soon afterward, the patient experienced an episode of aphasia. The neurological examination was unremarkable. A CT scan of the head showed signs of macrovascular encephalopathy. While hospitalized the patient suffered from vivid hallucinosis as well as from palinopsia, oblique vision, and prosopagnosia.

Conclusion: This patient suffered from severe visual hallucinations due to macrovascular encephalopathy in the thalamic region and in the pons. The visual hallucinations can be distinguished into two major groups, real hallucinations and pseudohallucinations. In contrast to real hallucinations the patient with pseudohallucinations is aware of the fact that his experiences are not real. Therefore pseudohallucinations, such as peduncular hallucinosis, are disturbing but most often are not very frightening to the patient. Visual pseudohallucinations often present with well formed and shaped pictures. In the case of peduncular hallucinosis they often appear micropptic. Oblique vision as an example of real hallucination is very confusing for the patient. This is reflected by the fact that it can result in gait difficulty. It is frequently encountered in brain stem strokes and brain stem syndromes, such as Wallenberg syndrome. In addition to pseudohallucination of the peduncular hallucinosis type and palinopsia this patient suffered from a visual neglect syndrome, prosopagnosia. The combination of pseudohallucinosis, real hallucinosis and visual neglect has not been previously described in a single patient to the best of the author’s knowledge. Concepts pertaining to the pathophysiology will be discussed.

CLINICAL AND GENETIC ANALYSIS OF X-LINKED NYSTAGMUS (NYS1)
J. B. Kerrison, R. Giorda, T. D. Lenart, A. Drack, I. H. Maunenee; Lackland AFB, Texas

Introduction: Familial congenital idiopathic nystagmus may be inherited in an autosomal dominant or X-linked pattern. Linkage analysis has identified three loci responsible for congenital nystagmus: 6p12 (NYS2, OMIM*164100), Xp11.4–p11.3, and 9q26–q27 (NYS1, OMIM *310700).

Objective: The present study investigated a family with congenital nystagmus inherited in an X-linked pattern using linkage analysis.

Methods: Clinical examination, genotyping of 30 individuals with markers from Xq26–q27 followed by linkage analysis, and sequencing of brain mitochondrial carrier protein-1 (BMCP1), which is expressed in the brain and located within the region of interest, in four affected individuals from four families linked to this region.

Results: The pattern of inheritance in the family was consistent with X-linkage with incomplete penetrance among carrier females. No affected males had affected sons. Based on the extended pedigree, the penetrance among obligate female carriers (daughters of affected males) was 24% percent (5 of 21).

Visual acuity among 16 affected individuals ranged from 20/20 to 20/70 (median 20/30). Clinical examinations, including electroretinography in two individuals, were otherwise normal except for the presence of nystagmus. Significant LOD scores (q = 0) were found with markers DXS8057, DXS8044, DXS1047, DXS1062, DXS8072, and DXS8078, placing the gene within a 5 cM interval flanked by DXS999 and DXS1211 on the distal long arm of the X chromosome. Sequencing the 10 exons of BMCP1 in four affected individuals from four families linked to this region failed to reveal any mutations.

Conclusions: NYS1 appears to be the most common cause of familial congenital idiopathic nystagmus. Linkage analysis of this family further reduces in interval in which NYS1 is located.

OPTIC NEURITIS FOLLOWING ANTHRAX VACCINATION
J. B. Kerrison, D. Lounsbury, G. Lane, M. Schatz, R. Engler; Lackland AFB, Texas

Objective: To report the occurrence of optic neuritis following anthrax vaccination in two patients.

Background: Bacillus anthracis is a biologic weapon threat because of its stability in spore form, its ease of culture, the absence of natural immunity in industrialized nations, and the severity of infection in its gastrointestinal and pulmonary forms. At least seventeen nations are suspected of developing offensive biologic weapons programs. Anthrax vaccine adsorbed (AVA), licensed by the FDA in 1970 and consisting of a six dose primary series, has been administered to United States servicemen as part of a Department of Defense initiative to protect against the threat of anthrax biologic weapons.

Methods: Description of clinical history, examination, neuroimaging, and further studies in two patients experiencing optic neuritis in temporal association with anthrax vaccination.
**Results:** Two patients, 39 and 23 years of age, presented with acute optic neuritis one month and two weeks, respectively, following anthrax booster vaccination and successfully treated with intravenous methylprednisolone. The first patient had a typical presentation and course of unilateral, retrobulbar optic neuritis with excellent visual recovery. The second patient presented with a bilateral anterior optic neuritis but has required chronic immunosuppression to maintain his vision. Retinal and optic nerve autoantibodies were present in the second patient. **Conclusion:** Optic neuritis is a potential adverse reaction of anthrax vaccination.

**MONOZYGOTIC TWINS WITH BILATERAL NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY**

**T. J. Carlow, C. L. Keys; Albuquerque, New Mexico**

**Objective:** To report the occurrence of nonarteritic anterior ischemic optic neuropathy (NAAION) in monozygotic twin brothers.

**Method:** A 71-year-old twin first noted painless visual loss on the left in 1960 and then presented in Albuquerque with decreased vision on the right in 1990. He reported that his ophthalmologist had documented a swollen left optic nerve in 1960. His brother, from Falls Church, VA, was first observed to have a visual field defect on the right and a pale right optic nerve during a routine examination in 1990 and then developed painless loss of vision in the left in 1997.

**Results:** The first twin’s visual acuity in 1990 was OD 20/80 and OS 20/20. Humphrey perimetry documented a significant superior and inferior deficit on the right and inferior altitudinal defect on the left. The right optic nerve was pale and swollen with splinter hemorrhages when he was initially examined in 1990, and the left nerve was flat and pale. Both optic nerves eventually became atrophic with a cup to disc ratio of OD 0.4 and OS 0.5. ESR and CRP were normal, and he had no symptoms of temporal arteritis. He had a history of a CABG in 1990, hypertension, angina, and hypercholesterolemia but no diabetes mellitus.

The second twin had visual acuities of OD 20/20 and OS 20/20 when he was examined for visual loss on the left in Falls Church, VA, in 1997. Humphrey perimetry documented bilateral inferior altitudinal visual field defects and a swollen left optic nerve. Both nerves were pale superiorly after the edema resolved, and the cup to disc ratio was 0.1 bilaterally. He had a history of an MI in 1977, a CABG in 1994, and hypercholesterolemia but no hypertension or diabetes mellitus. His history was negative for temporal arteritis and his ESR was normal.

**Conclusion:** NAAION can occur in monozygotic twins. Familial NAAION has been reported in six families; all cases were limited to siblings. One of these families included monozygotic twins with bilateral NAAION. DNA analysis will be required to determine if a chromosomal defect is at least partially responsible for this rare form of NAAION.

R. John Leigh, MD

Lea Averbuch-Heller, MD, died in an accident in Israel on September 26, 2000. Lea was known to many of us in the international neuro-ophthalmologic community for her clear presentations, encyclopedic memory, and high energy.

She was born in 1958 in St. Petersburg (Leningrad), Russia. Her grandfather was a psychiatrist who collaborated with the anatomist Bechterew. Her grandmother was a descendant of Anton Rubinstein, founder of the St. Petersburg Conservatory of Music. She was educated at the English high school in St. Petersburg and, during her childhood, had the opportunity to meet great musicians and poets of the Soviet Union. Her father was a psychiatrist, who got Lea interested in the neurosciences at an early age. She immigrated with her family to Israel in 1976. She studied Medicine at the Hebrew University-Hadassah Medical School, Jerusalem, where she also trained in neurology.

In 1992, she met Dr. Robert Daroff when he was a visiting professor at Hadassah Medical School, and he arranged for her to train in neuro-ophthalmology in Cleveland. She spent a year as an Ocular Motor Fellow, and then 2 years as a Clinical Neuro-ophthalmology Fellow, under the supervision of Bernd F. Remler, MD. She became Assistant Professor of Neurology at Case Western Reserve University in 1996. While in Cleveland (1993-98), she wrote more than 25 scientific papers and several chapters, including one on nystagmus for the fifth edition of Walsh and Hoyt’s Clinical Neuro-Ophthalmology. She developed a career as an independent researcher and won a grant from the National Institutes of Health.

In 1998, she returned to Israel and joined the faculty of Tel Aviv University–Sackler Faculty of Medicine, working at Rabin Medical Center under the chairmanship of Professor Eldad Melamed. She won a research grant from the German–Israeli Foundation for Scientific Research and Development and, at the time of her death, was preparing to begin experiments in the eye movement laboratory, which she had organized.

Lea was the essence of the clinician–scientist. Her powers of observation and her organized analytic mind made her an excellent clinician. She had a keen interest in nystagmus and led a clinical trial that demonstrated the effectiveness of gabapentin in patients with acquired pendular nystagmus. She spent several months working with Dr. David Zee and his colleagues at Johns Hopkins University, studying the effects of prism adaptation. In collaboration with Professor Jean Büttner-Ennever and her colleagues in Munich, Germany, she defined the clinical and pathologic features of a variant of amyotrophic lateral sclerosis with slow saccades. Along with her colleague, John Stahl, she demonstrated how pallidotomy for Parkinson disease caused saccadic intrusions. With characteristic clarity, she reinterpreted aspects of the neural control of eyelid movements, combining careful clinical observation with modern neurobiology.

It is hard to believe that Lea has left us because she was always so alive with her razor-sharp mind, timely humor, and cultured intellect. She seemed to know all art, literature, and music; linguistics was a hobby (she spoke four languages). She is survived by her husband, Moshe, and three young children. Her influence on those...
who knew her, and her contributions to neuro-ophthalmology, will long survive her tragically premature death.

SELECTED BIBLIOGRAPHY OF LEA AVERBUCH-HELLER, MD


