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What is Vasculitis?

Stephen E. Nadeau, MD

This issue of the Journal of Neuro-Ophthalmology includes two articles on temporal arteritis that emphasize problematic issues in the pathogenesis, diagnosis, and treatment of vascular inflammation. Cockerham et al (1) describe a patient with nonspecific orbital inflammation associated with biopsy-documented temporal arteritis whose ocular manifestations responded to radiation therapy. This article reminds us that vasculitis in general, temporal arteritis included, is a final common pathway of poorly understood immunopathologic processes that reflect the nature of the inciting antigen(s) and the immunogenetic profile of the patient (2). Kim et al (3) describe two episodes of late ipsilateral ischemic optic neuropathy caused by temporal arteritis in an apparently adequately treated patient, highlighting the uncertainties in our approach to treatment of this condition.

Our current approach to the diagnosis and treatment of vasculitis has its roots in the pathologically-based classification system developed by Zeek and Knowles (4,5) in the early 1950s. This nosology fortuitously corresponded to recognizable clinical syndromes. However, as science has advanced, the “lumps” defined by Zeek and Knowles have been successively split. The splits have had important therapeutic implications, as in the example of polyarteritis nodosa (PAN). Early on, Churg-Strauss disease, once classified as a PAN subtype, was split from the PAN group because of its distinctive features of prominent pulmonary manifestations, a history of allergies and crescendo asthma, an eosinophilic vascular infiltrate, peripheral eosinophilia, and high serum levels of IgE. Later, it was recognized that 30% of cases of "typical" PAN are related to chronic hepatitis B infection (a figure reduced to 10% since the advent of hepatitis B vaccine). More recently, it has become evident that many cases of PAN, including the form limited to nerve and muscle, are related to hepatitis C infection (typically in association with cryoglobulinemia), HIV infection, or a paraneoplastic disorder. Originally considered a vascular inflammation stemming from the deposition of antigen-antibody complexes in vascular walls with activation of complement and leukocyte chemotaxis, PAN is now recognized as considerably more complicated and variable, often involving cell-mediated immune processes. Most recently, it has been subdivided into a classic form and a far more prevalent form—microscopic polyangiitis (MPA). MPA is marked by prominent pulmonary involvement (with pulmonary hemorrhage), glomerulonephritis, association with p-ANCA (perinuclear pattern of antibodies to neutrophil cytoplasmic antigens), and a particularly malignant and refractory course requiring prolonged and aggressive immunosuppressive treatment.

The high morbidity and even mortality (intercurrent infection and secondary neoplasia) associated with corticosteroid and daily cyclophosphamide treatment of PAN pioneered by Fauci et al (6) in the early 1970s has led to a search for more specific therapies. Monthly pulsed intravenous cyclophosphamide treatment is now acknowledged to be as effective as daily cyclophosphamide in the treatment of idiopathic PAN, and it has lower morbidity. PAN related to hepatitis B, C, or HIV is best treated primarily with antiviral therapy.
This nosologic splitting process has also affected giant cell arthritis to the extent that temporal arteritis is differentiated from Takayasu's arteritis, a disorder with identical vascular pathology and spectrum of vascular involvement. Unlike temporal arteritis, Takayasu's arteritis predominantly affects the young, is particularly prevalent in Asia, and produces symptoms related to aortic branch arterial stenoses rather than inflammation of external carotid artery branches. These two disorders could reflect essentially the same immunopathologic process as it affects subjects with fundamentally different immunophenotypes. Cases such as that reported by Cockerham et al (1) remind us that the vascular pathology of temporal arteritis may occur in a variety of settings. It is quite possible that their patient did not have precisely the same disease as the patient with more typical temporal arteritis, or that the immunologic process leading to nonspecific orbital inflammation in this patient led, in addition, to temporal arteritis, or even vice versa.

Temporal artery biopsy should not be regarded as a convenient and effective approach to the tissue diagnosis of any and all kinds of vasculitis. The temporal artery may be involved by nearly any arteritis. However, biopsy of sural nerve, muscle, or viscera (such as the kidney or lung), or visceral angiography in the case of PAN, have far greater sensitivity and specificity than temporal artery biopsy for other vasculitides. Furthermore, the finding of inflammation in a temporal artery might lead to an incorrect diagnosis of temporal arteritis and exclusive reliance on corticosteroids when treatment with antiviral agents or cyclophosphamide is actually indicated.

Advances in the molecular biology of immune function are beginning to shed light on the pathogenesis of temporal arteritis and the closely related disorder, polymyalgia rheumatica (PMR) (7–12). Sixty percent of patients with temporal arteritis or PMR express the HLA-DR4 haplotype (defining a specific glycoprotein antigen receptor), compared with 30% of controls, and HLA-DR4-negative patients share an increased frequency of HLA-DR3, DR8 and DR13 haplotypes. Temporal arteritis, PMR, and rheumatoid arthritis share a strong association with certain allelic variants at the third hypervariable region on one of the genes (HLA-DRB1) that defines the shape of the HLA-DR4 antigen binding site—HLA-DRB1*0401 and *0404/8. However, the serologic specificity of HLA-DR4 in temporal arteritis and PMR is determined by sequence polymorphisms (allelic variants characterized by certain specific nucleotide sequences) at another hypervariable region within the HLA-DRB1 gene, one that defines the shape of another part of the HLA-DR4 antigen binding site. Patients expressing HLA-DR4 who have temporal arteritis or PMR exhibit specific allelic variants that produce characteristically shaped pockets within the antigen-binding cleft of the HLA-DR4 molecule. These pockets accommodate only antigens bearing very specific side chains. Once a macrophage encounters an antigen of the requisite shape and binding properties, it is able to present both that antigen and the CD80 or CD86 molecules on its surface to helper T-cells. These T-cells have an antigen receptor; they also have a receptor for CD80/86 (the CD28 molecule). Only when the macrophage presents the appropriate molecule to both T-cell receptors will a T-cell produce interleukin 2 (IL-2) and other cytokines that then induce the lymphoproliferative clonal expansion that begins the immune response. In temporal arteritis and PMR, this response appears to be entirely T cell-mediated. Unfortunately, the inciting antigen has not yet been identified.

Topographic studies of the immune process within the arterial wall of temporal artery biopsies in patients with temporal arteritis and PMR are providing information that may lead to identification of the antigen and are clarifying the inflammatory response. Among patients with both temporal arteritis and PMR, the majority of monocytes in the peripheral circulation are activated, as are the CD4 helper T-cells in arterial walls. However, only in the presence of actual arteritis is there evidence of further differentiation of these CD4 helper T cells, accompanied by the secretion of interleukin-2 (IL-2) and interferon-γ (IFγ). IL-2 induces clonal expansion of T cells and IFγ is a potent macrophage activator. The activation of these T cells apparently occurs through cytokine-mediated cross talk with local macrophages that have bound and presented the inciting antigen. The difference between the activated T cells in the arterial walls of patients with PMR and temporal arteritis is that in PMR, the T cells do not secrete IFγ. In temporal arteritis, these T cells are located primarily in the adventitia (apparently having migrated from the vasa vasorum), implicating the adventitia as the source of the inciting antigen. The cytokines produced by these cells, most particularly IFγ, attract another type of macrophage, which congregates in the media about the internal elastic lamina and secretes matrix metalloproteinases, which play a major role in tissue destruction. In some patients, macrophages expressing inducible nitric oxide synthase are attracted to the intima; nitration may contribute to tissue injury through lipid peroxidation. multinucleated giant cells, which develop in the media through unknown mechanisms, produce platelet derived growth factor (PDGF), which is chemotactic for the adventitial fibroblasts and medial myoblasts that generate intimal proliferation, and vascular endothelial growth factor, which induces angiogenesis. Intimal proliferation (without thrombosis) is the principal factor responsible for ischemic symptoms in temporal arteritis. Production of large amounts of arterial PDGF has been correlated with ischemic events such as visual loss, jaw claudication, and
stroke. Temporal arteritis is thus the emergent product of a complex interaction between specific immune events involving T-cells and several different types of macrophages and the microanatomic structure of the arterial wall.

The complexity of the immunopathologic process underlying temporal arteritis makes it easy to imagine how allelic variations, particularly in the HLA region, could lead to differences in clinical presentation, association with other disease processes, and treatability. The specificity of this clinical-immunopathologic link has recently been dramatically demonstrated in the delineation of a subtype of temporal arteritis that predominantly involves branches of the aortic arch and produces symptoms of upper extremity claudication rather than manifestations of ischemia and infarction in branches of the external carotid artery (13). This disorder affects the elderly, women more often than men (as in typical temporal arteritis), and it is as often associated with PMR (that is, it is not Takayasu's arteritis). However, temporal arteritis biopsy is negative in 42% of these patients, and the course is more insidious and less marked by tissue infarction as large vessel collaterals have time to develop. These clinical differences correspond to immunopathologic differences. The aortic arch variant is characterized by higher arterial levels of IL-2 RNA and it is associated with the HLA-DRB1*0404 haplotype, whereas typical temporal arteritis is more often associated with the HLA-DRB1*0401 haplotype. These discoveries start to explain the inconsistent clinical manifestations of temporal arteritis and the mediocre sensitivity of temporal biopsy—about 70% (14), which makes diagnosis so difficult.

Treatment of temporal arteritis has also been tendentious. In general, this condition is exquisitely corticosteroid-sensitive; there is evidence that starting prednisone doses as low as 20 mg daily may be adequate (15). However, it is equally clear that treatment must be very prolonged—up to 5 years in 40% of cases (16). The need for prolonged treatment may be related to the fact that corticosteroids suppress macrophage function but they do not suppress IL-γ producing T-cells, which are instrumental in instigating the disease process. Relapse may occur with apparently adequate corticosteroid dosage, as reported by Kim et al (3), but 90% of relapses occur with prednisone doses of less than 10 mg/day. There is emerging evidence of differences in corticosteroid requirements that may reflect underlying pathogenic mechanisms (17). Levels of the proinflammatory cytokine IL-6, which is released by antigen-presenting macrophages in arteritis lesions, may be a more sensitive marker of disease activity than the sedimentation rate (18). Unfortunately, this assay is not widely available.

Although it is less toxic, alternate-day corticosteroid treatment has been shown to be less effective than daily treatment (19). Corticosteroid-sparing agents such as azathioprine can usefully supplement but not replace corticosteroid treatment (20). Corticosteroid complications vary markedly from patient to patient, reflecting sex, comorbid conditions (weight, osteoporosis, hypertension, diabetes, peptic ulcer disease, infection), and individual idiosyncrasies. Treatment must involve a careful balancing of degree of confidence in diagnosis, awareness of possible diagnostic alternatives, individual corticosteroid side effects, and the probability of relapse. Where this balance is struck will remain a matter of clinical judgment until we have more sensitive and specific markers of the disease process.

Cockerham et al (1) used orbital radiation as an alternative to corticosteroid treatment in their patient with nonspecific orbital inflammation. This would not be the first time that radiation has been used to treat a local inflammatory or even vasculitic condition; it is the recommended treatment of lethal midline granuloma, likely a cross between Wegener granulomatosis and lymphomatoid granulomatosis, a type of lymphoma. The wisdom of this action will only be revealed as Cockerham et al (1) follow their patient to see if systemic corticosteroids need to be reinstituted and if there are long-term complications of radiation.

Advances in the management of temporal arteritis over the past 50 years have been based on earlier case ascertainment as a result of more widespread awareness of its prevalence and protean manifestations and by the emergence of an appreciation for its chronicity. Further advances will depend on understanding the full spectrum of temporal arteritis variants, which reflect a complex and variable immunopathogenesis, and the development of treatments specifically linked to discrete immunologic mechanisms.

REFERENCES
Radiosensitive Orbital Inflammation Associated with Temporal Arteritis

Kimberly P. Cockerham, MD, Glenn C. Cockerham, MD, Henry G. Brown, MD, and Ahmed A. Hidayat, MD

Abstract: A 75-year-old woman developed acute loss of vision in the OD, ipsilateral periorcular pain, an afferent pupillary defect, sectoral optic disc edema, and later ipsilateral proptosis and an intraconal mass. She denied any symptoms of temporal arteritis, and a sedimentation rate was normal. Orbital biopsy demonstrated chronic granulomatous inflammation with perivasculitis. A temporal artery biopsy disclosed findings consistent with temporal arteritis. Following 2000 cGy of external beam radiation, her visual function and orbitopathy completely resolved. This unusual presentation of orbital inflammation in association with temporal arteritis demonstrates that pathologic findings of temporal arteritis may be clinically nonspecific and that external beam radiation may be an effective therapy in this setting.

(J Neuro-Ophthalmol 2003;23: 117-121)

Orbital inflammation may be isolated (nonspecific orbital inflammation), or associated with systemic inflammation such as Wegener granulomatosis, polyarteritis nodosa, sarcoidosis, or, rarely, temporal arteritis (1-22). Nonspecific orbital inflammation is classically acute in onset but may be recurrent. On pathologic inspection, a mixed inflammatory infiltrate without epithelioid cells is typically present. Orbital inflammation associated with systemic disease is commonly subacute and bilateral. Diagnosis is often difficult, as laboratory evaluation findings may be negative for a specific disorder and systemic involvement can occur decades later.

Temporal arteritis classically appears in patients of at least 65 years of age with new-onset headache, jaw claudication, anterior ischemic optic neuropathy, myalgias, fatigue, and weight loss. Temporal artery tenderness and elevated sedimentation rate are characteristic. Neuro-ophthalmic manifestations also include posterior ischemic optic neuropathy, central retinal or cilioretinal artery occlusion, and cranial neuropathies. Orbital manifestations include orbital ischemic syndrome and, very rarely, orbital inflammation (1-9). The orbital inflammation is often corticosteroid-responsive, but visual loss may occur despite immunosuppressive therapy (5). Radiation therapy has not been previously considered.

CASE REPORT

A 75-year-old woman noticed acute visual loss and periorcular pain in the OD. She denied weight loss, anorexia, muscle aches, jaw claudication, or temporal tenderness. She had had elevated cholesterol controlled with gemfibrozil; there was no history of hypertension or diabetes and she was a nonsmoker.

Visual acuity was 20/70 OD and 20/20 OS. A right afferent pupillary defect, sectoral optic disc edema, and an inferotemporal visual field defect were noted (Fig. 1). Westergren erythrocyte sedimentation rate was 27 mm/h. A diagnosis of nonarteritic ischemic optic neuropathy was made, and the patient was placed on daily aspirin.

The patient returned 2 months later with improvement in her visual acuity to 20/20 OD and resolution of her periorcular pain. One month later, she reported worsening vision and periorcular pain. She still denied other symptoms of temporal arteritis. Visual acuity had fallen to finger counting OD and 20/20 OS. She had an afferent pupillary defect OD. The optic disc edema had improved but the right visual field had worsened (Fig. 2). A repeat erythrocyte sedimentation rate was 29 (C-reactive protein <0.1).

The patient was treated with prednisone 80 mg/d. A temporal artery biopsy, performed 10 days later, was reported to be negative for temporal arteritis, so her prednisone was tapered over 2 weeks.
When the patient returned 1 month later, having been completely weaned off corticosteroid medication for 2 weeks, visual acuity had improved to 20/60 OD and remained 20/20 OS. But she now demonstrated 3 mm of right axial proptosis and inferior scleral show (Fig. 3). Her right periocular ache had returned following the corticosteroid

![FIG. 3. Four months after presentation, right proptosis with inferior scleral show has developed.](image)

![FIG. 4. Axial computed tomography scan shows a homogeneous apical orbital mass that extends through the superior orbital fissure.](image)

![FIG. 5. Orbital biopsy shows chronic inflammatory cells surrounding an artery (arrow) within the orbital tissue. Most of the inflammatory cells are mature lymphocytes (hematoxylin-eosin, magnification x320.).](image)

FIG. 1. Humphrey 30-2 visual field at presentation demonstrates defects with a nerve fiber bundle configuration and temporal hemianopic features, consistent with apical optic nerve involvement (mean deviation -8.45 dB).

FIG. 2. Humphrey 30-2 visual field 3 months later shows deterioration (mean deviation -16.53 dB).

FIG. 3. Four months after presentation, right proptosis with inferior scleral show has developed.
RADIOSENSITIVE ORBITAL INFLAMMATION


FIG. 6. Temporal artery biopsy. **A:** Granulomatous inflammation is present within the adventitia and outer media. Numerous epithelioid cells are seen (arrow); no multinucleated giant cells were present. The intima was not inflamed (hematoxylin-eosin, magnification ×320). **B:** Higher power view demonstrates fibrous scar in the area of disruption of the internal elastic lamina. Minimal inflammation is present (Masson trichrome stain). **C:** Special staining for elastin demonstrates disruption of the internal elastic lamina associated with scarring of the inner position of the vessel wall (Verhoeff-van Giessen stain).

The patient was intolerant to the side effects of continued oral corticosteroid treatment, so external beam radiation was performed (2000 cGy over 2 weeks). One month after irradiation, orbitopathic signs had disappeared (Fig. 7) and visual function had returned to normal (Fig. 8).

DISCUSSION

We have described a case of granulomatous orbital inflammation resulting in compressive optic neuropathy.
TABLE 1. **American College of Rheumatology 1990 criteria for the diagnosis of temporal arteritis**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset &gt;50 years</td>
<td></td>
</tr>
<tr>
<td>New onset or type of localized head pain</td>
<td></td>
</tr>
<tr>
<td>Temporal artery tenderness or decreased pulsation</td>
<td></td>
</tr>
<tr>
<td>ESR &gt;50 mm/hour (Westergren)</td>
<td></td>
</tr>
<tr>
<td>Temporal artery vasculitis characterized by any of the following:</td>
<td></td>
</tr>
<tr>
<td>Mononuclear cell infiltration</td>
<td></td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
<td></td>
</tr>
<tr>
<td>Multinucleated giant cells</td>
<td></td>
</tr>
</tbody>
</table>

*At least three criteria must be present for diagnosis. ESR, erythrocyte sedimentation rate.

The patient also demonstrated pathologic evidence of temporal arteritis but had only some of the typical clinical manifestations of that condition (Table 1).

Several vasculitides have been implicated in orbital inflammation. Wegener granulomatosis and polyarteritis nodosa are candidates, as both entities have also been noted to cause a granulomatous vasculitis of the temporal artery with and without giant cells. Fibrinoid necrosis, if present, is characteristic of these entities, but the pathologic features affecting the temporal artery can be indistinguishable from those of temporal arteritis (1–5).

Could our patient have had Wegener granulomatosis? We consider it unlikely because the c-ANCA was normal and there was a lack of sinus or pulmonary findings (14,15). However, cANCA-negative orbital inflammation is a diagnostic possibility. Polyarteritis nodosa would seem an unlikely diagnosis in the absence of p-ANCA positivity and without renal, neurologic, or skeletal muscle involvement (16–22). If our patient had temporal arteritis, she had a very atypical variant. Visual recovery and orbital involvement are rare. Reported sites of orbital involvement include the extracocular muscles, optic nerve sheath, and intraconal fat (Table 2). Most patients, especially those with isolated extracocular muscle involvement, have demonstrated resolution of their orbital symptoms and signs with oral corticosteroid treatment. In the one case with an intraconal lesion similar to our case, permanent visual loss occurred despite corticosteroid and cyclophosphamide therapy (1–10).

This case highlights the lack of clinical specificity of the pathologic findings of temporal arteritis and the potential utility of temporal artery biopsy in the face of an inaccessible orbital mass. Moreover, we believe that it is the first report of granulomatous orbital inflammation associated with temporal arteritis in which radiation therapy produced full recovery.

TABLE 2. **Orbital masses associated with arteritis of the temporal artery**

<table>
<thead>
<tr>
<th>Study</th>
<th>Age/gender</th>
<th>Orbital signs</th>
<th>Imaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chertok et al (3)</td>
<td>67/F</td>
<td>Ptosis</td>
<td>Enhancing SR mass (CT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevation deficit</td>
<td></td>
</tr>
<tr>
<td>Nassani et al (4)</td>
<td>69/F</td>
<td>Proptosis</td>
<td>Irregular ONS, Abnormal intraconal fat (CT)</td>
</tr>
<tr>
<td>Lee et al (5)</td>
<td>70/M</td>
<td>Visual loss*</td>
<td>Infiltrative lesions*</td>
</tr>
<tr>
<td></td>
<td>69/M</td>
<td>Diplopia</td>
<td>Enhancing ONS (MRI)</td>
</tr>
<tr>
<td></td>
<td>72/F</td>
<td>Pain, proptosis</td>
<td>Enhancing MR mass (MRI)</td>
</tr>
<tr>
<td></td>
<td>82/F</td>
<td>Proptosis, Episcleritis</td>
<td>Increased EOM size (MRI)</td>
</tr>
<tr>
<td>Cockerham (current article)</td>
<td>75/F</td>
<td>Pain, visual loss, proptosis</td>
<td>Intracanal mass (CT)</td>
</tr>
</tbody>
</table>

*Bilateral.

CT, computer tomography; EOM, extraocular muscle; MR, medial rectus; MRI, magnetic resonance imaging; ONS, optic nerve sheath; SR, superior rectus.

REFERENCES

Late Ipsilateral Recurrence of Ischemic Optic Neuropathy in Giant Cell Arteritis

Nancy Kim, PhD, Jonathan D. Trobe, MD, Andrew Flint, MD, and Gary Keoleian, MD

Abstract: A patient with arteriosclerosis, diabetes mellitus, and giant cell arteritis (GCA) treated continuously with low-dose prednisone developed anterior ischemic optic neuropathy (AION) at 5 and 13 months after clinical diagnosis of GCA. At the time of late recurrent AION, there were no systemic symptoms or elevations in acute phase reactants to signal active arteritis, yet temporal artery biopsy disclosed dramatic inflammation, forcing the presumption that the infarct was arteritic. Recurrent systemic symptoms and elevation of acute phase reactants are not reliable warning signs of reactivated GCA. In patients at high risk for corticosteroid complications, late biopsy may be a reasonable guide to corticosteroid weaning.

(J Neuro-Ophthalmol 2003;23: 122-126)

Giant cell arteritis (GCA) is a systemic, necrotizing vasculitis of the elderly primarily affecting large and medium size cranial arteries originating from the aorta (1-3). It presents with fever, myalgia, malaise, weight loss, headache, temporal or scalp tenderness, jaw claudication, and acute, painless visual loss (4), the most serious complication. Typically, the cause of visual loss is anterior ischemic neuropathy (AION) secondary to inflammatory occlusion of the short posterior ciliary arteries supplying the laminar and retrolaminar regions of the optic disk (4-7).

The accepted treatment of GCA is intravenous methylprednisolone at 1 to 2 g/d for 3 to 5 days or oral prednisone at 1 to 2 mg/kg/d for the initial 2 to 4 weeks pending clinical improvement and normalization of acute phase reactants (erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP]), followed by a slow prednisone taper to a baseline dose that suppresses reactivation of symptoms and elevation of acute phase reactants (8-10).

Once the systemic symptoms and acute phase reactants have normalized, future episodes of AION are relatively uncommon (9,11-13). Late recurrent visual loss in the ipsilateral eye is even rarer (9,11-13). Recurrent symptoms generally include malaise, weight loss, and myalgia, headache, or scalp tenderness (9,14-18). We present a case in which prednisone therapy failed to prevent AION at 5 and 13 months after initial diagnosis without any recrudescence in systemic symptoms or elevation in acute phase reactants. Temporal artery biopsy, performed at the time of the recurrent ipsilateral AION, was floridly positive.

CASE REPORT

In October 2000, an 83-year-old man presented to his primary care physician with a several day history of severe headache, arthralgia, and myalgia. He had longstanding hypertension, noninsulin-dependent diabetes mellitus, and hyperlipidemia. Thirty years earlier, he had experienced sudden severe and permanent visual loss in the OS that had been attributed to a retinal artery occlusion. He had no abnormalities in the OD. Physical examination was normal. Westergren ESR was 101 mm/h and CRP was 15.4 mg/dl. MRI and MRA of the brain showed remote, focal ischemic injury but no vessel abnormalities.

Based on the symptoms and marked elevation in acute phase reactants, a presumptive diagnosis of GCA was made and the patient was begun on prednisone 60 mg/d (Fig. 1). No temporal artery biopsy was performed at this time. Within a few days, the patient's symptoms had completely resolved. Over the next 6 weeks, prednisone was tapered to 20 mg/d with good symptom control and reduction of the ESR to 10 mm/h. Because of the patient's ample arteriosclerotic risk factors, he was considered highly vulnerable to corticosteroid complications. Therefore, within 2 months after clinical diagnosis of GCA, the prednisone dose had been further reduced to 20 mg every other day.

The patient remained asymptomatic on this maintenance dose until 5 months after diagnosis, in early March 2001, when he suddenly developed acute visual loss in the OD. At that time, systemic medications also included digoxin 0.25 mg/d, amlopidine besylate 5 mg/d, metoprolol 50 mg/d, furosemide 40 mg/d, metformin hydrochloride,
and simvastatin 20 mg/d without recent dosage changes. Blood pressure was 170/85, pulse 60 and regular, and there were no cardiac or cervical auscultatory abnormalities.

Ophthalmologic examination disclosed visual acu­ties of 20/30 OD, 20/200 OS. No afferent pupillary defect was present in the OD. Ophthalmoscopy revealed a swollen superior optic disk OD and a corresponding inferior altitudinal visual field defect (Fig. 2). The left fundus appeared unchanged. ESR and CRP at this time were 27 mm/h and 0.5 mg/dl, considered within the normal range. He received a presumptive diagnosis of arteritic AION and the prednisone dose was increased to 60 mg/d. The prednisone was gradually tapered over the next 6 months to 10 mg/d as the ESR and CRP remained normal (Fig 1).

In late November 2001, 13 months after his original diagnosis and 8 months after the development of AION in the OD, the patient developed recurrent acute visual loss in that eye. He denied any symptoms compatible with systemic hypotension, and no major drop in blood pressure had been recorded. Visual acuity had fallen from 20/25 to 20/50 OD and an afferent pupil defect was now apparent. The visual field disclosed extension of the defect superiorly. Swelling of the optic disk was again observed, this time in the inferior segment (Fig. 3). Prednisone was increased to 60 mg/d. A temporal artery biopsy obtained a week later revealed dramatic inflammatory infiltration of the vessel with giant cells, histiocytes, and lymphocytes, as well as severe destruction of the internal elastica (Fig. 4).

In June 2002, 7 months after the second attack of arteritic AION OD, examination disclosed stable visual acu­ties of OD 20/50, OS 20/200 with a pale disc OD. The patient had been slowly tapered to a dose of prednisone 10 mg/d. ESR was 2 mm/h.

**DISCUSSION**

Despite continuous low-dose maintenance prednisone therapy, our patient developed two attacks of AION.
in the same eye at 5 and 13 months after initial clinical diagnosis of GCA. Because of the floridly positive biopsy for GCA at 13 months, we presume that each attack represented arteritic rather than nonarteritic vaso-occlusion. Yet there was no recurrence of systemic symptoms or rise in acute phase reactants to signal a flare-up.

A normal ESR at presentation does not preclude the diagnosis of GCA (19-21). In a retrospective series, Ellis and Ralston (22) found that 18 (23%) of 80 patients in a population treated for GCA had presented with an ESR within the normal range. Monitoring acute phase reactants may also be an ineffectual means of detecting GCA recurrence. A long-term study of 77 GCA patients who had an initial ESR higher than 30 mm/hr (23) found that clinical relapses late in the course of treatment were associated with an elevated ESR in only 43% of cases and an elevation of CRP in only 35% of cases. While there have been a number of investigations of other inflammatory mediators as potential markers of GCA disease activity (24-26), no clearly reliable alternatives have emerged.

Our patient’s visual relapse occurred not only without a rise in acute phase reactants, but also without warning symptoms. Most relapses during long-term treatment of GCA consist of fever, malaise, myalgias, jaw claudication, scalp tenderness, or temporal headache (9,14-18). Late visual loss is uncommon and prior reports of this phenomenon do not provide adequate documentation regarding concurrent corticosteroid doses, systemic symptoms, or acute phase reactants (9,11-13,27).

In a series of 45 GCA patients, Liu et al (11) described six in whom AION occurred at 1 month to 6 years after presentation and the initiation of corticosteroid treatment. In three patients, prednisone doses were 10 to 40 mg/d at the time of visual loss. In a fourth patient, prednisone was 5 mg taken on alternate days. In the fifth patient, the prednisone had been discontinued 1 week before the visual loss; no dose information is available for the sixth patient. ESR was elevated in only three patients at the time of late visual loss. There is no information regarding systemic symptoms accompanying these events.

Late ipsilateral recurrence of AION in patients with GCA is very rare. Calamia and Hunder (12) described a patient who experienced recurrent ipsilateral visual loss 5 months after initiation of treatment with prednisone 25 mg/d. At the time of the initial episode of visual loss, ophthalmologic examination revealed an afferent pupillary defect OD, a visual acuity of 14/21, and slight blurring of the right nasal optic disc margin. At the time of the recurrent ipsilateral visual loss, visual acuity had worsened to finger counting OD, but no further clinical details are provided. However, visual acuity returned to baseline OD with an increase in the prednisone dose to 60 mg/d.

In their review of GCA cases, Liu et al (11) reported recurrent AION in the same eye in two patients (patients #8, #10) at 8 months and 14 months after initiation of continuous prednisone therapy. Patient #8 was taking prednisone 5 mg/d at the time of visual recurrence. However, other information regarding the presence or absence of recurrent
ISCHEMIC OPTIC NEUROPATHY


symptoms, laboratory findings, or corticosteroid dosages is not provided.

Was our patient's recurrent ipsilateral AION really the result of arteritic occlusion, or was it a nonarteritic occlusion in a patient with ample arteriosclerotic risk factors? Given that recurrent NAION in the same eye is extraordinarily rare, that no systemic hypertensive episodes were documented, and that the temporal artery biopsy showed dramatically active inflammation, we are persuaded that arteritis accounted for the recurrence.

This case illustrates a context in which late biopsy could be useful. There are few other reports regarding late biopsy in the diagnosis and management of GCA. Guevara et al (18) reported a patient with recurrence of systemic symptoms 4 months after starting prednisone therapy (initial dose 60 mg/day). The prednisone dose at the time of relapse was 30 mg/d and ESR was within normal limits. No temporal artery biopsy had been obtained at original diagnosis. A biopsy obtained 2 months following the emergence of these new symptoms showed an active, diffuse inflammatory infiltrate and giant cells centered at the internal elastic. No further information regarding subsequent follow up is available in this report.

Cohen (9) described nine patients in whom recurrent systemic symptoms or elevations in ESR occurred each time corticosteroid taper was attempted, despite a year of continuous oral prednisone therapy (initial dose 40–100 mg/day). Because several patients had already experienced corticosteroid complications (Cushing syndrome, gastrointestinal bleeding, osteoporosis), each received a repeat biopsy at 1 year after diagnosis to better determine which patients had persistent active arteritis. Four patients in this group had a negative biopsy (vessel fibrosis but no active inflammatory infiltrate or giant cells) and were tapered off prednisone. None had any recurrence of symptoms or elevated ESR during a follow-up period ranging from 5 months to 2 years. The remaining five patients had active histopathology (diffuse intramural inflammatory infiltrate with giant cells and destruction of the internal elastic). Of these, one patient discontinued corticosteroid therapy at the time of biopsy and had a prompt escalation of systemic symptoms and increased ESR that resolved when treatment was restarted. The other four biopsy-positive patients were continued on prednisone treatment of another year. Three patients in this group, as well as the patient who had briefly discontinued therapy, were subsequently tapered from prednisone without recurrence of GCA after a follow-up of at least 5 months. The remaining patient continued to demonstrate an intermittently elevated ESR with each attempt at reducing the prednisone. One year after the second biopsy, he underwent a third temporal artery biopsy. It was negative, so he was tapered off prednisone without a relapse after 2 years of follow-up. These studies (9,18) suggest that late biopsy may be useful in indicating whether prednisone therapy should be continued despite its many serious side effects.

Although we acknowledge that late arteritic AION is rare, our case emphasizes that it may occur even when corticosteroid treatment has eliminated systemic symptoms and normalized acute phase reactants. These indicators are evidently not an adequate guide to long-term treatment. The fact that visual loss and a floridly positive biopsy were documented 13 months after diagnosis in our case supports an accumulating anecdotal literature suggesting that patients may need to be protected with higher prednisone doses for well over 1 year in GCA. In patients who are vulnerable to corticosteroid side effects, where corticosteroids must be tapered relatively quickly, late biopsy may be a reasonable option in guiding the tapering process.

REFERENCES


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Linear Magnetic Resonance Enhancement and Optic Neuropathy in Primary Angiitis of the Central Nervous System

Adam S. Hassan, MD, Jonathan D. Trobe, MD, Paul E. McKeever, MD, and Stephen S. Gebarski, MD

Abstract: A 38-year-old woman developed incoherent mentation, tremor, ataxia, and bilateral optic disc edema with mildly depressed visual acuity, nerve fiber bundle defects, and a left afferent pupillary defect. Magnetic resonance imaging of the brain disclosed striking linear contrast enhancement radiating from the ventricular borders. Lumbar puncture showed a normal opening pressure with a lymphocytic pleocytosis and elevated protein. On the basis of these findings, the initial diagnosis was viral or post-viral meningoencephalitis and the patient was not treated. During the next 4 weeks, her condition worsened. A brain and meningeal biopsy disclosed findings typical of primary angiitis of the central nervous system. With aggressive treatment, her neurologic status and magnetic resonance imaging normalized and her optic neuropathy improved markedly. Optic neuropathy and linear magnetic resonance imaging enhancement should be recognized as features of primary angiitis of the central nervous system.

Primary angiitis of the central nervous system (PACNS) is a rare disease of unclear etiology that manifests clinically with headache, altered mentation, and a variety of focal neurologic deficits (1). Magnetic resonance imaging (MRI) typically reveals multifocal white and gray matter signal abnormalities. Leptomeningeal enhancement may uncommonly occur (2). We present a case in which the MRI abnormalities displayed a rarely reported pattern, a radial distribution of contrast enhancement that corresponded to inflamed cerebral vessels and perivascular regions. Our patient also had bilateral optic disc edema with optic nerve dysfunction yet normal intracranial pressure, features not previously well documented in PACNS.

CASE REPORT

A 38-year-old woman developed nausea, vomiting, diarrhea, myalgias, and generalized weakness in early January 2002. Within 1 week, symptoms evolved into incoherent mentation, extremity tremor, incoordination of limbs, and balance difficulty. Examination disclosed inattention, resting tremor of the extremities, slight extremity ataxia, and mild tandem gait difficulty.

Her medical history included depression, paroxysmal atrial tachycardia, and hyperlipidemia. Medications included digoxin and an oral contraceptive.

Standard laboratory and toxicologic studies were negative. Brain MRI revealed diffuse abnormal contrast enhancement distributed in a linear pattern radiating from the ventricular borders into the deep white matter with surrounding T2 signal alteration. There was less striking abnormal enhancement of the leptomeninges (Fig. 1). The subcortical white matter and gray matter were relatively spared.

A lumbar puncture showed an opening pressure of 150 mm Hg with 250 white blood cells, mostly lymphocytes, a normal glucose, a slightly elevated protein at 50 mg/dl, elevated myelin basic protein, no oligoclonal bands, and a negative cytologic study for malignancy. Polymerase chain reaction for herpes simplex and cultures of the cerebrospinal fluid, as well as serologies for rheumatologic, vasculitic, paraneoplastic, and peroxisomal disorders, were negative. The patient was given a diagnosis of viral or post-viral meningoencephalitis, and was discharged home without treatment.

On examination 1 month later, the patient had greater confusion and tremor, and was complaining of decreased vision in the OS. Visual acuity was 20/25 OU. Pupils were equal in size, and reacted normally to direct light with an afferent defect in the OS. Ocular ductions were full with...
smooth pursuit and no nystagmus. The eyes were aligned. The anterior ocular segments were normal. Ophthalmoscopy disclosed moderate bilateral optic disc edema (Fig. 2). Formal visual fields could not be performed because of poor cooperation. She was fearful, inattentive, disoriented to time, unable to remember more than two of three objects, or to remember any objects after 3 minutes. She had a shaking tremor of the head, trunk, and extremities. Deep tendon reflexes were 3+ throughout. The rest of the neurologic examination was normal.

Brain MRI showed the same abnormalities noted 5 weeks earlier. A lumbar puncture had an opening pressure of 180 mm Hg and the fluid contained 150 white blood cells, a glucose of 75 mg/dl, and a protein of 121 mg/dl. Serologic studies identical to those performed on the earlier admission were negative. On the fifth hospital day, she became unresponsive except to deep painful stimuli, and an electroencephalogram disclosed diffuse seizure activity consistent with status epilepticus. Phenytoin treatment eliminated the seizure activity within 24 hours and restored the patient’s baseline mentation.

Biopsy of the right frontal cerebral cortex, underlying white matter, and overlying meninges revealed inflammation in and around vascular walls (Fig. 3A). Immunohistochemical stains for CD3, CD20, CD45, and CD68 revealed polyclonal inflammation in which T-lymphocytes predominated and B-lymphocytes and macrophages were common. Many inflammatory cells infiltrated the walls of small vessels (Fig. 3B–D). While primarily vasocentric, a few cells occurred in brain parenchyma (Fig. 3B,C). Intense gliosis indicated that the lesion was more than 2 weeks old (Fig. 3E). These features substantiated the pathologic diagnosis of PACNS.

The patient was treated with intravenous methylprednisolone 1 gm/d for 3 days, followed by prednisone 60 mg/d and intravenous cyclophosphamide 125 mg/d followed by oral cyclophosphamide 125 mg/d. Within a month, her mentation had improved dramatically and her tremor had become less pronounced. Visual acuity was 20/25 OD, 20/30 OS, optic disc edema had lessened, and visual fields disclosed nerve fiber bundle defects binocularly, denser in the OS (mean deviation -3.44 dB OD, -5.71 dB OS) (Fig 2). During the ensuing weeks, her mentation returned to normal and her tremor disappeared. At 6 months after illness onset, visual acuity had improved to 20/20 OD, 20/25 OS, the left afferent pupil defect persisted, the optic disc edema had virtually disappeared, but visual fields still showed a defect in the OS (Fig 2). MRI abnormalities, both on T2 and T1 enhanced sequences, had completely resolved (Fig. 4).
DISCUSSION

Two features of our patient's PACNS have not been well documented: the linear MRI enhancement and the optic neuropathy.

Although MRI abnormalities are present in over 95% of histologically confirmed cases of PACNS (3,4), they are only 36% specific to PACNS (5). The most common findings are focal signals abnormalities with characteristics of multiple bilateral cerebral infarcts involving gray and deep white matter (6,7). Leptomeningeal enhancement may be associated with the parenchymal lesions (2) or be an isolated MRI finding (8). Less commonly, signal abnormalities have been reported to involve only the deep white matter (6,9). Our patient's MRI revealed striking linear contrast enhancement radiating from the ventricles into the deep white matter, distributed in a pattern suggestive of disease in the perivascular regions with surrounding T2 signal alterations. One published case (10) reported similar MRI findings, but they are less dramatic than in our case. The diffusion-weighted sequence did not suggest infarction. Instead, these MRI findings indicate severe but reversible perivascular inflammation causing blood-brain barrier disruption and injury of surrounding white matter. The radial distribution of these enhancing signal abnormalities follows the path of vessels. Likely to be specific for vasculitis, this configuration is not seen in the MRI scans of patients with multiple sclerosis or post-viral demyelination, which show ring-like, lobular, or fusiform signal abnormalities.

Optic disc edema has been rarely described in PACNS. In the six reported cases, patients all had well-documented elevation of intracranial pressure (11–16), as distinct from our patient, whose intracranial pressure was normal. There is one reported case of "bilateral optic atrophy" without further detail (20). Four cases of bilateral visual loss have been described secondary to cortical infarction (17–19). Our patient likely had vasculitic inflammation.
of the optic nerves equivalent to the process within the cerebrum. These abnormalities have not been reported in PACNS. The relative sparing of visual acuity suggests an "optic perineuritis" pattern, in which inflammation may be concentrated in the perioptic meninges. Curiously, had the optic neuropathy with disc edema been noted earlier in our patient, it might have given further support to the initial—and mistaken—diagnosis of post-viral demyelination, in which optic neuropathy is common.

In reporting this case, we wish to emphasize that these MRI and optic disc findings should not be presumed to be signs of a primary demyelinating illness, in which treatment may not reverse the deficits, but should prompt a consideration of PACNS, in which aggressive treatment may restore vision and be life-saving.

REFERENCES

Persistent Severe Visual and Electroretinographic Abnormalities After Intravenous Cisplatin Therapy

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Abstract: A 55-year-old man inadvertently received four times the intended dose of intravenous cisplatin as part of a chemotherapeutic salvage regimen for non-Hodgkin lymphoma. Immediately after treatment, he developed bilateral irreversible visual loss. Visual acuity was 20/300 in OU and visual fields showed central scotomas bilaterally. Although the fundus examination findings were normal, an electroretinogram showed markedly reduced a-wave amplitudes and absent b-waves. At autopsy 8 months later, photoreceptors appeared normal. Splitting of the outer plexiform layer was present, consistent with loss of the ERG b-wave. This is the first reported case of persistent visual loss from intravenous cisplatin toxicity and the first case to describe ocular histopathologic findings.

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Many cases of intermediate- and high-grade non-Hodgkin lymphomas (NHL) respond to combination chemotherapy. For recurrent disease, salvage regimens offer an opportunity for a second remission but little chance for long-term control. Salvage regimens are often complicated and may involve continuous infusions of some agents. These regimens use maximally tolerated doses, so there is little margin for error. Well-publicized examples of dosage errors have been reported in the lay press.

We report a case in which a patient received cisplatin as part of a salvage regimen for NHL. Because of a dosage miscalculation, he received four times the planned dose of cisplatin before referral to our institution. Consequently, he suffered severe, permanent vision loss due to cisplatin-induced retinal toxicity. We report the first case of persistent visual loss in this setting and document the retinal abnormalities found on autopsy.

CASE REPORT

A 55-year-old man developed night sweats, weight loss, and a nonproductive cough. Cervical and intra-abdominal lymphadenopathy were discovered and a biopsy revealed a diffuse large cell lymphoma, B-cell phenotype. He received six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy and achieved a complete remission.

Four months later, the patient developed bilateral axillary and retroperitoneal lymphadenopathy. He received ESHAP (cisplatin, etoposide, high-dose cytarabine, and methylprednisolone) chemotherapy. The planned regimen included a 4-day continuous infusion of cisplatin at a dose of 25 mg/m² daily for a total cisplatin dose of 100 mg/m² over 96 hours. The actual delivered cisplatin dose was 100 mg/m² daily for 4 days, or 400 mg/m² total dose.

Two days after the conclusion of chemotherapy, he was admitted to the hospital with anorexia, nausea, tinnitus, decreased vision, and loss of color perception. He was found to have acute renal failure, visual impairment, severe hepatotoxicity, and pancytopenia. Following a 1-month hospitalization, he was referred to the University of Utah for further care.

Best-corrected visual acuity was 20/300 in OU and the patient was unable to identify any of the Hardy-Rand-Rittler color plates. He had no congenital color vision deficit by history. Pupils were normally reactive and there was no afferent pupillary defect. He had a central scotoma in OU by confrontation and extraocular motility was full. Anterior segments were quiet with mild nuclear sclerosis and posterior subcapsular cataract. Intraocular pressures were normal. Fundus examination was normal except for a choroidal nevus in the temporal periphery of the OD. There was no optic nerve edema or pallor and no visible abnormalities of the macular retinal pigment epithelium. Goldmann visual field testing revealed mild, generalized constriction and...
central scotomas in OU, as well as an inferior arcuate scotoma in the OD.

His physical examination revealed no evidence of lymphoma. He had a dense, bilateral, stocking-glove neuropathy to pinprick and vibration and his deep tendon reflexes were diminished. An electroretinogram (ERG) revealed diminished a-wave amplitudes and complete loss of the b-wave. Magnetic resonance imaging of the brain showed no lymphomatous involvement of the brain, meninges, or orbits, or any other pathologic lesion of the central visual pathways.

Six months later, the patient developed progressive cervical and supraclavicular adenopathy. He received cyclophosphamide, etoposide, procarbazine, and prednisone. His adenopathy promptly resolved but his neurologic deficits remained unchanged. Two months later, he died of clostridial sepsis. At 6 weeks prior to death, his visual acuity was unchanged at 20/300 in OU. Both globes were obtained at autopsy and examined by an ocular pathologist (NM).

On gross pathologic examination, the globes appeared completely normal. On microscopic examination, the retina showed artefactual detachment secondary to processing and cutting. The ganglion cell layer was mildly attenuated temporally, being approximately three to four cell layers thick. The inner nuclear layer also showed some irregularity with a decrease in cell thickness from approximately four or five cell layers to approximately two cell layers in some sections. The outer plexiform layer showed a small amount of splitting. The outer nuclear layer and photoreceptor outer segments were normal. Sections of the optic nerve were stained for both axons and myelin, and all sections appeared normal. In the general autopsy examination, there were no abnormalities of the central visual pathways.

**DISCUSSION**

Cisplatin (cis-dichlorodiammine platinum [II]) is used in the treatment of both systemic and central nervous system malignancies and is thought to exert its biologic effect by binding directly to DNA. The major toxic effects of cisplatin are nephrotoxicity, ototoxicity, and a peripheral neuropathy. Irreversible vision loss may result from effects on the retina, optic nerve, or cortical visual pathways.

Retinal toxicity has been reported after therapeutic, high-dose intravenous administration of cisplatin and can be associated with pigmentary changes in the macula. Widing et al. (3) studied 13 patients receiving high-dose intravenous cisplatin (200 mg/m$^2$ in five divided daily doses over two to four cycles). Eight patients reported blurred vision and three of these patients also described altered color perception. Nine of 11 patients studied had ERG abnormalities. During the follow-up period, symptoms of blurred vision gradually dissipated, although three patients continued to note altered color perception, and abnormalities in the ERG persisted. Unfortunately, data regarding visual acuity were not reported, although the authors implied that no patients had persistent, significant visual impairments.

By contrast, intracarotid infusion of cisplatin, occasionally used in the treatment of cerebral malignancies, can produce significant permanent visual impairment. Five series of patients experiencing visual loss associated with the intracarotid infusion of cisplatin have been reported (4-8). The pathophysiology of the visual loss was not completely understood.
investigated in every case, but it appears that visual loss can occur from effects on both the retina and the optic nerve. Although visual loss was typically ipsilateral to the placement of the infusion catheter, there are some patients who experienced bilateral visual impairment. In two series in which intracarotid infusion of cisplatin was accompanied by intravenous administration of carmustine (BCNU), some patients developed vision loss and an unusual pigmentary maculopathy (9,10). Because of its toxicity, intracarotid cisplatin is no longer in common use.

Marmor (11) reported a single case of vision loss associated with inadvertent intravenous cisplatin overdose. A 68-year-old woman being treated for ovarian cancer suffered loss of visual acuity after receiving 480 mg of cisplatin, roughly seven times the usual dose. Her acuity returned to normal, but she had persistent ERG abnormalities, including reduced b-waves and oscillatory potentials, and a pigmentary maculopathy.

The only previous report of cisplatin-associated vision loss with autopsy material (12) involved a 3 1/2-year-old girl treated with cisplatin for a sacrococcygeal teratoma. The patient initially received five cycles of cisplatin, 120 mg/m². In the course of treatment, she developed bilateral optic disc edema, bilateral hearing loss, renal toxicity, loss of muscle stretch reflexes, and a right foot drop. At autopsy, both optic nerve heads were swollen, but there was no comment about histopathologic examination of the retina or about axonal loss or alterations in myelination within the optic nerve. There was also no mention of visual acuity or funduscopic examination of the retina.

Although the ERG a-wave in our patient was substantially attenuated, the photoreceptors appeared normal on histopathologic examination. One could speculate that cisplatin is toxic to photoreceptor function, but that it does not always cause morphologic changes in the photoreceptors. Alternatively, because only 1 year had elapsed between the administration of cisplatin and the patient’s death, it is possible that photoreceptor degeneration would have occurred if given sufficient time. The splitting observed in the outer plexiform layer may explain the loss of the b-wave and the preservation of a small a-wave in both our patient and the patient described by Marmor (11). Splitting of the outer plexiform layer would result in the loss of transmission of signals between the photoreceptors and the inner retina. This alteration in the outer plexiform layer may also explain attenuation of the b-wave observed in some patients receiv-
ing intra-arterial cisplatin and carmustine (7). Other substances that are associated with selective or predominant decrease in b-wave amplitude include iron, methanol, quinine, vincristine, canthaxanthin, glycine, and vigabatrin (13). Loss of the b-wave has also been reported with an occupational exposure to the veterinary anesthetic ethyl-m-anilinobenzoic acid methanesulfonate (MS-222) (14).

Paraneoplastic antibodies, as in carcinoma-associated retinopathy (15) and melanoma-associated retinopathy (16), have been shown to cause severe, irreversible vision loss along with attenuation of the ERG. Our patient was not tested for the presence of antiretinal antibodies, which we considered an unlikely cause of his vision loss. First, these retinopathies are almost always associated with solid tumors and there is only one report in the literature of a slowly progressive, lymphoma-associated retinopathy (17). Second, patients with vision loss associated with paraneoplastic retinopathies usually describe photopsias and progressive loss of visual acuity, in contrast to our patient's abrupt, bilateral, simultaneous loss of vision.

Although retinal toxicity associated with both intravenous and intra-arterial cisplatin has been previously reported, this is the first case in which intravenous administration of cisplatin has been associated with severe retinal toxicity, enough to cause irreversible loss of vision. The fact that irreversible vision loss, previously associated only with intracarotid administration of cisplatin, can also occur with intravenous administration lends further support to the hypothesis that the toxic effects of cisplatin on the retina are dose-dependent (2). This case is also the first case in which histologic sections of retina have been obtained. The splitting observed in the outer plexiform layer may explain the loss of the b-wave documented in our patient, as well as in other patients receiving large amounts of cisplatin. The mechanism that causes this observed splitting is unknown.

REFERENCES

Surgical Management of Skew Deviation

R. Michael Siatkowski, MD, Robert F. Sanke, MD, and Bradley K. Farris, MD

Abstract: There are no published data on the outcomes of realignment surgery for skew deviation. A retrospective chart review disclosed 10 patients who had undergone surgical correction of skew deviation by three surgeons at a single institution between 1991 and 2002. Nine of 10 patients had satisfactory relief of diplopia with an acceptable field of single binocular vision. Vertical rectus recession or resection was the most common procedure. Four patients required more than one procedure. For nonalternating hypertropias, resection of the inferior rectus muscle or recession of the superior rectus muscle of the hypertropic eye was successful. For alternating hypertropia, resection of both inferior rectus muscles was successful. Oblique muscle surgery was not associated with good outcomes.

Methods

After appropriate University of Oklahoma Health Sciences Center Institutional Review Board approval, charts from 30 patients who were diagnosed with skew deviation between January 1991 and January 2002 were retrospectively reviewed. The diagnosis of skew deviation was made based on the presence of vertical diplopia following an ischemic, inflammatory, traumatic, degenerative, or neoplastic disorder affecting the supranuclear vertical eye movement centers in the brain stem. Cases with concomitant oculomotor or trochlear nerve paresis or orbital pathology (n = 10) were excluded. Ten candidates were excluded because fusion could not be achieved in primary gaze with prism correction. Thus, surgical subjects had no preoperative evidence of symptomatic subjective torsional diplopia or central disruption of fusion. After exclusions, there were 10 patients who met study criteria (Table 1). Their charts were reviewed for age and gender of the patient, initial strabismic measurements, cause of the misalignment, surgical procedure or procedures performed, final ocular alignment, and the patients' assessment of whether they were satisfied with the surgical results.

Results

The age range for the 10 study patients was 31 to 83 years, with a mean of 57 years (Table 1). Six patients were female. The causes of skew deviation were brain stem stroke (n = 6), mesencephalic mass lesion (n = 1), spinocerebellar degeneration (n = 1), lithium toxicity (n = 1), and ethanol toxicity (n = 1).
None of the 10 patients had a successful surgical outcome, six after one procedure, two after two procedures, and one after three procedures. There was one surgical failure, in a patient who underwent two procedures.

Most patients (81–7, 10) had nonalternating hypertropias; three of them (#1, 5, 10) had relatively comitant misalignment, and five (#2, 3, 4, 6, 7) had misalignment patterns that mimicked a unilateral inferior rectus paresis, with a nonalternating hypertropia worsening on ipsilateral gaze. Two patients (#8, 9) had alternating hypertropias mimicking bilateral inferior rectus pareses. Surgical results for these three patterns are discussed separately.

Relatively Comitant Nonalternating Hypertropia (Patients #1, 5, 10)

Patient #1 had a strictly comitant vertical deviation successfully treated with resection of the inferior rectus of the hypertropic eye. A small preoperative exodeviation disappeared after surgery, perhaps because of increased horizontal fusion ability after the vertical deviation had resolved, or perhaps because of the improved tertiary additive effect of the strengthened inferior rectus. Inferior rectus resection was chosen over superior rectus recession because the largest misalignment was in downgaze and abduction, the field of action of the inferior rectus.

Patients #5 and #10 had large concomitant horizontal misalignments in addition to hypertropia. Patient #5 had bilateral sixth nerve pareses, and patient #10 had a comitant exotropia. Patient #10 had resolution of the vertical deviation after a horizontal recess-resect procedure with superior transposition of the horizontal recti to correct the vertical misalignment. The transposition was performed to limit surgery to one eye and to avoid the potential of anterior segment ischemia.

Patient #5 required three procedures. The first consisted of a unilateral horizontal recess-resect procedure for esotropia, combined with an ipsilateral inferior oblique resection to correct 10 prism-diopters of hypertropia. The choice of inferior oblique surgery was made to attempt to achieve a successful result with surgery by operating on only one eye, and to avoid the potential of anterior segment ischemia. This resulted in a significant vertical overcorrection, however, requiring two recessions of the contralateral superior rectus. Two additional procedures (including chemodenervation of a medial rectus) were also required for the esotropia caused by sixth nerve pareses, but the final postoperative outcome was satisfactory.

Nonalternating Hypertropia Mimicking Ipsilateral Inferior Rectus Paresis (Patients #2, 3, 4, 6, 7)

Patients #2, 4, 6, and 7 had successful results after a single surgery. Three patients had resections of the inferior rectus of the hypertropic eye, and one had a recession of the superior rectus of the hypertropic eye (patient #7). Resections of the inferior rectus were performed more frequently than superior rectus recessions because the misalignment was greatest in downgaze and abduction, and surgery on the muscle working in this field of action was desired. However, both strategies had equal success.

Patient #3 had a postoperative vertical overcorrection after inferior rectus resection and also reported cyclorotation of the hypertropic eye. Strengthening the anterior fibers of the superior oblique tendon was attempted for this but resulted in worsening vertical and torsional misalignment. It was speculated that the superior oblique tendon had slipped after the second procedure, but the patient refused further surgery. This case constituted the only surgical failure.

Alternating Hypertropia Mimicking Bilateral Inferior Rectus Pareses (Patients #8, 9)

Both patients (#8, 9) initially underwent bilateral inferior rectus resections and each remained undercorrected with symptomatic vertical diplopia on side gaze after the first procedure. Patient #8 had a second procedure consisting of bilateral superior rectus recessions, and patient #9 had a re-resection of one inferior rectus muscle. Both had an improved field of single binocular vision and notable subjective improvement after the second surgery.

Despite surgical manipulation of the vertical recti, no patients had a significant A- or V-pattern strabismus postoperatively. Additionally, none had subjective cosmetic or functional problems regarding lid position following surgery, presumably because of intraoperative dissection of the inferior rectus from the lower lid retractors and dissection of the attachments of the superior rectus from the levator palpebrae superiors.

Adjustable sutures were used in three cases, twice during the first procedure (patients #5, 7) and once during a second procedure (patient #8). This technique was associated with a satisfactory outcome in each case.

Further details of surgical procedures and outcomes are presented in Table 1.

DISCUSSION

Vertical misalignment of the visual axes following damage to the supranuclear control areas for ocular movement is termed the Magendie-Hertwig syndrome, or skew deviation (1). Coordinated ocular movements are the result of inputs to the ocular motor nuclei from the vestibular system, brain stem, and cerebellum, with the vestibulo-ocular reflex playing a crucial role in these activities (5–8). Skew deviation results from unilateral or asymmetric disruption
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TABLE 1. Continued

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IRHT                  | 8RHT 8ET              | 10RHT           | Unsatisfied          |

|                      | 8XT 2XT 1RHT 1XT      | 4XT             | Satisfied            |

LSR Recess 5.0         | LSR Recess 2.0         | 12ET 2LHT 10ET  | Satisfied            |

LLR Resect 5.0         | LLR Resect 5.0         | 3LHT            |                      |

LLR Resect 7.0         | Botulinum toxin LMR   | 2ET             |                      |

Lsr Recess 5.0*        | RSR Recess 10.0*      | 8RHT 6ET        | Satisfied            |

RIR Reresect 3.5       | 1LHT A                | 2LHT 2ET        | Satisfied            |

Misalignment measured in prism diopters; extraocular muscle procedures measured in millimeters.

* Adjustable suture; superior transposition. A, aligned.

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of the central graviceptive input in the roll plane as it ascends from the tectrices to the interstitial nucleus of Cajal in the mesencephalon (9, 10). This nucleus maintains tonic innervation of motor neurons that supply the extraocular muscles controlling vertical and cyclotorsional movements. Skew deviation may be a component of the triad known as the ocular tilt reaction, which consists of vertical deviation, head tilt, and conjugate torsion of the globes to the same side (11–14).

Skew deviation may manifest as a comitant or fairly comitant nonalternating vertical misalignment with varying amounts of torsion. When isolated and not accompanied by significant horizontal misalignment, conventional vertical rectus muscle recession or resection using standard surgical doses (2–3 prism diopters of realignment per millimeter of muscle recession or resection) sufficed in 9 of our 10 cases.

Surgical planning is significantly complicated when large horizontal deviations are also present. We had one success with simple vertical transposition of the horizontal recti for a small hypertropia (patient #10), but in the authors’ experience, this technique is not likely be effective in correcting vertical misalignments of greater than 8 to 10 prism-diopters. In the case with bilateral abducens pareses (patient #5), in which inferior oblique recession was performed, there was a large vertical overcorrection that we cannot fully explain. This occurrence, combined with the comparative success of vertical rectus muscle surgery, however, has significantly lessened our enthusiasm for oblique muscle surgery in the patterns of skew deviation discussed in this paper.

For patients with nonalternating, incomitant hypertropias mimicking a unilateral inferior rectus paresis, standard-dose vertical rectus muscle surgery was generally effective. We preferred inferior rectus recession to superior rectus recession because the deviation was greater in downgaze, but in one case (patient #7), the surgical procedure was a superior rectus recession, after which the patient did well. Another potential advantage of inferior rectus recession over superior rectus recession is the effect on postoperative eyelid position. When the inferior rectus is dissected from the lower lid retractors and subsequently resected in the amounts used in our patients (all 5 mm or less), there is no significant superior displacement of the lower eyelid. However, even with dissection of the attachments between the superior rectus and the levator, lid retraction may occur, and in a patient who also now has decreased upgaze, exposure keratopathy may result.

For patients with alternating hypertropias mimicking bilateral inferior rectus pareses (15, 16), bilateral vertical rectus muscle surgery is required. However, our two patients with this pattern (patients #8, 9) were initially undercorrected and required a second procedure, even though the degree of hypertropia was not significantly different from that of the patients with nonalternating hypertropias (patients #2, 3, 4, 6, and 7), who generally did well with a single surgery. This may support augmentation of initial surgical doses for correction of this type of skew deviation.

For skew deviation mimicking unilateral or bilateral inferior rectus paresis, one could argue that weakening of the superior oblique muscle of the hypertropic eye could be just as effective as inferior rectus recession of the hypertropic eye. In fact, Hamed (17) has argued that many patients with A-pattern strabismus originally believed to be due to primary superior oblique overaction actually have skew deviation. However, superior oblique weakening procedures such as tenotomy or tenectomy are less predictable and more difficult to quantify than inferior rectus surgery. They are also likely to produce symptomatic excyclotorsional diplopia in patients who have no symptomatic preoperative torsional complaints. In addition, superior oblique procedures are generally more technically difficult than inferior rectus procedures. Even the use of a superior oblique tendon expander, which may be more quantifiable than tenectomy or tenotomy, can be unpredictable and produce restrictive motility deficits postoperatively.

A weakness of this report is lack of consistent pre- and postoperative information on torsional status and head tilt. However, we selected for surgery only those patients who could fuse with prisms and had no symptomatic torsional diplopia preoperatively. When encountering patients with notable torsional complaints, it is likely that oblique muscle surgery would be required, as these muscles are the major cyclotorters of the eye. However, smaller amounts of torsion, perhaps up to 10 degrees, may be treated with vertical rectus muscle surgery, since inferior rectus resection or superior rectus resection will produce relative postoperative excyclotorsion, and inferior rectus recession and/or superior rectus resection will produce relative postoperative incyclotorsion (18). In addition, with time, both torsional and vertical fixation amplitudes, as well as head tilt, may improve because of central nervous system adaptation (19). Nine of our patients were subjectively satisfied postoperatively, indicating that symptomatic torsional diplopia was not present.

Our single clear surgical failure was, in our opinion, most likely due to a slipped muscle rather than misjudgement in patient or procedure selection. In general, we believe that vertical rectus muscle surgery is effective in patients with skew deviation who lack substantial torsional complaints. When diplopia was not significantly relieved with surgery alone, the misalignment had been reduced sufficiently and made more comitant such that small amounts of prism could alleviate diplopia in primary and reading positions. Although a 40% reoperation rate may seem high, this is comparable to a reoperation rate of approximately one third in infantile esotropia (20).
Skew deviation is frequently associated with other, often severely compromising, neurologic changes following damage to the vestibular, cerebellar, and brain stem areas. Improving the patient’s vision to its maximal potential can be quite significant, particularly for patients with balance or coordination difficulties. For these patients, even partial improvement of diplopia can provide a major functional advantage. Our experience shows that strabismus surgery can greatly improve the patient’s ocular alignment and quality of life. We encourage physicians to consider such surgery in the management of appropriately selected patients with skew deviation.

REFERENCES
Progressive Visual Loss Because of a Suprasellar Pneumatocele After Trans-sphenoidal Resection of a Pituitary Adenoma

Andrew G. Lee, MD, John C. Van Gilder, MD, and Matthew L. White, MD

Abstract: A 63-year-old man who underwent uneventful trans-sphenoidal resection of a pituitary adenoma with fat packing complained postoperatively of progressive binocular visual acuity loss. Neuroimaging showed a suprasellar pneumatocele compressing the optic chiasm and a communication between the sphenoid sinus and the sella. After a second trans-sphenoidal procedure to remove the air and fully pack the sphenoid sinus, visual acuity recovered dramatically. A rare complication of trans-sphenoidal surgery for pituitary adenoma, suprasellar pneumatocele probably forms through a ball-valve mechanism that results from incomplete packing of the sellar floor. This case highlights the need for effective sphenoid sinus packing and for ophthalmic monitoring after trans-sphenoidal surgery.

Case Report

A 63-year-old man developed painless, progressive visual loss OU. He had impotence for the past several years and was found to have a low serum testosterone level. Magnetic resonance imaging (MRI) showed an intrasellar mass with suprasellar extension (Fig. 1).

The preoperative visual acuity was 20/60 OD and 20/20 OS, and an automated visual field test (Humphrey 30-2) showed an almost complete bitemporal hemianopia (Fig. 2). The patient underwent uncomplicated trans-sphenoidal surgery. During the procedure, the mucosa of the sphenoid sinus was stripped entirely, the dura was incised, and the tumor was resected in a piecemeal fashion. After adequate decompression and tumor resection, abdominal wall fascia and fat were packed into the sella.

Postoperatively, the patient reported subjectively improved vision, but no formal ocular examination or visual field testing was performed. Four weeks after surgery, he complained of painless, progressive worsening of vision in both eyes.

FIG. 1. Preoperative enhanced T1-weighted coronal magnetic resonance imaging scan shows an intrasellar mass with suprasellar extension and elevation and flattening of the optic chiasm (arrow).
Neuro-ophthalmic examination 2 months after the surgery showed a visual acuity of 20/400 OU, and Goldmann visual field testing revealed a bitemporal hemianopia denser superiorly in the OD and more complete temporal hemianopic loss in the OS. (A Goldmann visual field test was performed rather than a repeat automated [Humphrey 30-2] field test because of the loss of central visual acuity OU and the desire to document the extent of peripheral field loss outside of 30 degrees.) There was mild optic disc pallor OU. A plain skull radiograph (Fig. 3), computed tomographic scan (Fig. 4), and MRI scan (Fig. 5) showed a large collection of air in the suprasellar space compressing the optic chiasm from below. The MRI showed that the packing did not completely bridge the gap between the sphenoid sinus and the sella.

The patient underwent a second trans-sphenoidal surgery in which the air was removed and a fat pack completely placed in the sphenoid sinus. Postoperatively, the patient’s visual function improved to 20/40 OD and 20/20 OS. The bitemporal hemianopia persisted (Fig. 6). A postoperative sagittal MRI scan showed restoration of chiasmal anatomy, absence of suprasellar air, and complete fat packing of the sphenoid sinus (Fig. 7).

**DISCUSSION**

We describe a patient who suffered progressive visual acuity loss attributed to compression of the optic chiasm by intracranial air under pressure (tension pneumocephalus, or pneumatocele). This is an extremely rare phenomenon.

One of us (JVG) has performed more than 2000 trans-sphenoidal surgeries, and this is the only case of postoperative suprasellar pneumatocele encountered. Haran and
FIG. 6. Automated visual field testing after the second trans-sphenoidal surgery to remove the pneumatocele and pack the sphenoid sinus shows a persistent bitemporal hemianopia. (The patient's visual acuity improved considerably.)

Chandry (4) reported only three cases of pneumocephalus among 300 trans-sphenoidal surgeries for pituitary macroadenoma or craniopharyngioma during a 12-year span (4). The authors postulated that air could enter the intracranial cavity through a cerebrospinal fluid (CSF) fistula at the skull base, a tendency that was exacerbated by decreased intracranial CSF pressure produced by a lumbar drain or ventriculoperitoneal shunt. In another case, the authors postulated that postoperative radiation therapy produced tumor shrinkage and an “uncorking effect,” leading to a secondary CSF leak and admission of air. The authors reported that re-exploration, repair of the sella, and re-packing of the sphenoid sinus with fat had to be performed in all three cases. They recommended reducing intracranial pressure by tapping ventricular air and draining the CSF, but only after repair of the CSF fistula.

Air under pressure can act as a mass lesion and produce compression on the optic pathway. Shehu and Ismail (1) presented a case of traumatic tension pneumocephalus associated with light perception vision in the OS, presumably from an acute compressive optic neuropathy. Although the reported ophthalmologic details of this case are insufficient to exclude a concomitant traumatic optic neuropathy, the patient “regained full vision” after surgical release of the tension pneumocephalus. Hayman et al (5) reported a case of headache, bitemporal hemianopsia, and a tension pneumocephalus following endoscopic surgery of the ethmoid and sphenoid sinuses. The authors initially postulated that the chiasmal visual loss may have been due to the pneumocephalus and ventricular dilation from trapping of air due to a ball-valve mechanism. The post-decompression MRI scan, however, showed chiasmal “hyperintense” signal, and the visual field did not recover (5).

To our knowledge, ours is the only case of suprasellar pneumatocele following trans-sphenoidal surgery causing reversible visual acuity loss. We presume that incomplete packing created an opening between the sphenoid sinus and the sella that allowed air to enter the suprasellar space, accounting for the slowly progressive nature of the visual acuity loss after initially successful surgery. The tension was created by trapping of the air within the confined space between the sellar floor, its lateral walls, and the umbrella of tumor capsule. The second surgery replaced the initial fat packing with new and more complete fat packing of the sinus and resolved the chiasmal compression. This improved the visual acuity dramatically, but the patient was left with residual bitemporal field loss. Our case highlights the importance of the proper amount of fat packing of the sphenoid sinus after trans-sphenoidal surgery—enough to prevent a pneumatocele but not too much to compress the optic chiasm. It also emphasizes the need for careful ophthalmic monitoring of vision in patients who have undergone trans-sphenoidal surgery.

REFERENCES

Environmental Tilt Illusion as the Only Symptom of a Thalamic Astrocytoma

Aric J. Aldridge, MD, Lanning B. Kline, MD, and Christopher A. Girkin, MD

Abstract: A 14-year-old girl experienced two episodes of environmental tilt illusion. During both episodes, which lasted less than 1 minute, she perceived all objects within view as rotated 45 degrees clockwise. There were no auras, accompanying symptoms, or sequelae. Neuro-ophtalmic examination findings were normal except for a right relative afferent pupil defect (RAPD). Imaging disclosed a cystic mass in the left posterior thalamus with compression of the brachium of the left superior colliculus. Stereotactic biopsy revealed a pilocytic astrocytoma. This is the first case documenting environmental tilt illusion as an isolated symptom of a thalamic lesion. Disruption of vestibular connections between the posterior thalamus and the posterior parietal cortex may be the cause of this visual perceptive disorder.

CASE REPORT

A 14-year-old girl reported two 30-second episodes of perceived environmental tilt. The first occurred at school as she approached the dining table and placed her lunchbox on it. She experienced a 45-degree clockwise rotation of the table such that her lunchbox appeared to lie on the floor. The entire room was noted to tilt during the episode. As she sat at the table, the rotation gradually resolved over a 30-second period. Several friends were with her during the event and none reported observing signs of seizure activity, loss of consciousness, or inappropriate behavior. In fact, the patient was entirely aware of what was happening for the duration of the episode. Approximately 5 months later, a second episode occurred in similar fashion at home with perceived rotation of the television set and room. The television set and objects around it rotated 45 degrees clockwise. During this episode, she "followed" the perceived rotation by leaning to her right until it began to reverse at a point when she was lying on her right side. The entire episode lasted approximately 30 seconds. Her father witnessed the event and noted no associated signs. As with the first episode, she was fully aware of the phenomenon and there were no auras, loss of consciousness, headache, seizure activity, vertigo, or other neurologic signs or symptoms.

Her medical and family histories were negative. Her only medication was loratadine (Claritin, Schering [U.S.]). She denied use of any psychotropic substances. General medical and neurologic examinations were unremarkable. Magnetic resonance imaging of the brain ommitted a cystic mass in the left posterior thalamus with compression of the brachium of the left superior colliculus (Fig. 1). Stereotactic biopsy of the lesion revealed a benign pilocytic astrocytoma (Fig. 2).

The patient was referred for neuro-ophtalmic consultation. Best-corrected visual acuity was 20/20 OU. Pupils measured 4 mm OU, briskly reactive to light with a right RAPD. Color vision was normal by Ishihara pseudoisochromatic plate testing, and visual fields were full by manual and automated (SITA-Standard) methods. Eye movements were intact, and anterior and posterior segment examination findings were within normal limits OU.

Management options offered to the patient and her parents included stereotactic radiosurgery or observation with serial MRI scanning. The family chose to observe with serial scans. Imaging studies and clinical examinations have remained stable over 20 months of follow-up.
Aldridge et al.

FIG. 1. A: Fluid-attenuated inversion recovery axial magnetic resonance imaging (MRI) scan demonstrates a mass lesion (arrow) in the left posterior thalamus in the region of the brachium of the superior colliculus, explaining the relative afferent pupil defect. B: Unenhanced T1-weighted sagittal MRI reveals the mass to have a cystic component (arrow).

DISCUSSION

Environmental tilt illusion, also known as tilt of the subjective visual vertical, is a disorder of visuospatial perception (1–4). This rare phenomenon has been reported to occur in association with pathologic lesions in seemingly disparate areas of the brain, such as the occipitoparietal cortex, medulla (in dorsolateral medullary stroke of Wallenberg), otolithic pathways in the peripheral vestibular organ, labyrinth, cerebellum, and thalamus. Potential causes include tumor, infection, infarction, trauma, multiple sclerosis, seizure, and migraine (1,10–14).

The cause of the environmental tilt illusion is unknown. Tiliket et al (3) have suggested that it may result from a disorder of integration of visuospatial input. This disorder could arise from a lesion at the level of the brain stem, with abnormal integration of visual and otolithic inputs, or at the cerebral cortex, where there might be an inability to integrate visual and somesthetic information. The posterior parietal cortex has been shown to contain an abstract representation of space constructed from integration of inputs from several sensory modalities (15–17). Pathologic lesions disrupting this area of higher order visuospatial processing can result in the phenomenon of visual environmental rotation (1).

In our patient, the lesion was confined to the posterior thalamus, a complex relay center interposed between sensory and motor loci within the brain. It is subdivided into six...
groups of nuclei, one of which is the largest and most posterior of the thalamic nuclei, the pulvinar, where our patient’s lesion was centered. The pulvinar receives afferent inputs from the superior colliculus, as well as the temporal, parietal, and occipital lobes, and sends efferent information to these three cerebral hemispheric lobes (18). Mapping studies in the macaque monkey have shown that the inferior and lateral posterior-pulvinar subnuclei contain a complete visuotopic representation of the contralateral visual field. The anterior inferior pulvinar receives inputs from the superior colliculus as well as corticothalamic projections from the primary visual cortex. It sends projections to extrastriate and inferotemporal areas. The lateral posterior-pulvinar complex also receives corticothalamic inputs from cortical areas containing visuotopic maps, including the primary visual cortex. It sends efferent projections primarily to the posterior parietal cortex (19).

Additional mapping studies in the rhesus and macaque species have localized the vestibular thalamic nuclei to the postero-lateral thalamus near the pulvinar. The specific subnuclei in the human believe to correlate most closely with those of these animals include the Vm (nucleus ventro-oralis intermedius), Vce (nucleus ventro-caudalis externus), Dc (nucleus dorsocaudalis), and Ve (nucleus ventro-caudalis internus) (2,20). Thalamic infarctions in this region have been shown to cause environmental tilt illusion in the absence of the other components of the optic tilt reaction (20).

The interaction of vestibular input with inputs from other sensory modalities has been demonstrated from the level of the vestibular nuclei in the brain stem to the thalamus and cortex. Mapping studies in the rhesus monkey have demonstrated vestibular input to a parietal area that may correspond to the vestibular area located within the human intraparietal sulcus of the posterior parietal cortex. Moreover, neurons in this region are known to be sensitive indicators of visual-field motion, demonstrating the role of vestibular input in spatial orientation (21). We suggest that disruption of vestibular connections between the posterior thalamus and the posterior parietal cortex is the cause of our patient’s visual perceptive disorder.

To our knowledge, this is the first case documenting visual tilt illusion in the absence of other neurologic findings (except for a RAPD) in the setting of an isolated lesion of the posterior thalamus. Other investigators have reported this illusory phenomenon in thalamic disorders, but the patients had other neurologic findings such as hemiparesis, hemisensory loss, or hemiataxia (20). More commonly, this illusion has arisen in the setting of lesions in the brain stem or cerebral cortex, areas previously incriminated as causing this phenomenon (22).

REFERENCES
Leptomeningeal Enhancement and Venous Abnormalities in Granulomatous Angiitis of the Central Nervous System

Janet C. Rucker, MD, Valérie Biousse, MD, and Nancy J. Newman, MD

Abstract: A 68-year-old woman with a relatively acute onset of right homonymous hemianopia, Gerstmann syndrome, and global cognitive failure was found to have a lymphocytic pleocytosis and elevated protein on spinal fluid examination and displayed marked meningeal enhancement on magnetic resonance imaging and dilated cortical venules on cerebral angiography. Brain and meningeal biopsy disclosed a necrotizing granulomatous inflammation of small and medium-sized subarachnoid vessels. The brain parenchyma was normal. The angiographic presence of venous abnormalities, the lack of observable angiographic arterial involvement, and the lack of parenchymal pathology are distinctly unusual in granulomatous angiitis of the central nervous system. This case, therefore, extends the pathologic and imaging spectrum of this disorder.


A 68-year-old, right-handed, white woman was noted by her husband to be bumping into walls. Within 3 hours, she complained of right-sided visual impairment and pain behind her left ear. She seemed to have difficulty pronouncing words. Twenty-four hours later, when examined in the emergency room, the visual impairment and confusion persisted, but language skills had returned to normal. On examination, she recalled none of three words after a delay of 5 minutes. She also displayed agraphia, acalculia, right/left disorientation, finger agnosia, difficulty following complex commands, and a right homonymous hemianopia. Computed tomography (CT) of the head, performed without contrast, demonstrated periventricular white matter hypodensities consistent with small vessel ischemic disease.
She was admitted to the neurology service and placed on intravenous heparin with the presumed diagnosis of acute cerebral ischemia. Despite therapeutic anticoagulation, she developed word finding difficulty and impaired comprehension. Magnetic resonance imaging (MRI) of the brain, performed 3 days after symptom onset, showed increased signal on FLAIR images in the convexity and sulcal spaces, most extensive over the left parietal lobe (Fig. 1A), and periventricular white matter chronic ischemic changes. T1 unenhanced images show subtle low intensity areas in the peritrigonal white matter (Fig. 1B). Postgadolinium images showed extensive enhancement of the leptomeninges (Fig. 1C). Diffusion-weighted MRI failed to show restricted diffusion, ruling out acute ischemia. Magnetic resonance angiography (MRA) showed normal intracranial and extracranial vessels.

Heparin was stopped and three consecutive lumbar punctures were performed, each with elevated opening pressure.
pressure (300–350 mm water), elevated protein (106–223 mg/dl), lymphocytic pleocytosis (8–38 white blood cells), and negative cytology and cultures. A four-vessel cerebral angiogram showed normal arterial vasculature (Fig. 2A). However, in the venous phase, there were prominent and tortuous superficial cortical venules, most extensive over the left parietal region (Fig. 2B). Meningeal and cortical biopsy, obtained because of worsening mental status, revealed an active granulomatous, necrotizing inflammation and fibrinoid necrosis of small and medium-sized vessels in the subarachnoid space. There was no evidence of parenchymal involvement (Fig. 3). Based on the biopsy results, the patient was diagnosed with granulomatous angiitis of the central nervous system (GANS) and treated aggressively with high-dose prednisone and cyclophosphamide. She had dramatic improvement in her neurologic status within days.

Granulomatous angiitis of the central nervous system (GANS), also called primary angiitis of the central nervous system or primary central nervous system vasculitis, is an idiopathic inflammatory disorder of small central nervous system leptomeningeal and parenchymal blood vessels (1). The typical MRI findings in GANS are multiple, bilateral, T2 and FLAIR high signal abnormalities in the cortex and deep white matter. Even when conventional MRI is normal, signals consistent with ischemia may be demonstrated on diffusion-weighted MRI (4). Only once has leptomeningeal enhancement been reported as the only MRI abnormality (3). In that case (3), the patient had acute onset of confusion and gait impairment, diffuse leptomeningeal enhancement on MRI, lymphocytic pleocytosis and elevated protein on cerebrospinal fluid examination, and a noninfectious granulomatous inflammation of subarachnoid vessels demonstrated on biopsy. However, that patient did not undergo cerebral angiography or diffusion-weighted imaging. Our patient’s diffusion-weighted imaging was normal, confirming lack of brain parenchymal ischemia. Moreover, there was no evidence of arteritis on conventional angiography. In fact, cerebral angiography is only 60% sensitive in pathologically documented cases of GANS; the “classic” findings of arteritis—alternating areas of stenosis and ectasia in multiple vascular distributions—occur in less than 40% of cases (2). The extensive abnormalities seen on the venous phase of our patient’s angiogram (Fig. 2B) are very unusual and appear to correlate with the leptomeningeal enhancement seen on MRI. This finding likely represents either venous inflammation or localized venous dilation secondary to the overlying leptomeningeal inflammation.

REFERENCES

Giant Cavernous Malformation of the Occipital Lobe

Carlos Filipe Chicani, MD, Neil R. Miller, MD, and Rafael J. Tamargo, MD

Abstract: A 15-year-old boy who developed severe headaches and an incomplete homonymous hemianopia was found to have a large, well-circumscribed, multilobulated intracranial mass in the contralateral occipital lobe. The initial impression was that of a low-grade glioma or a vascular malformation. When the lesion increased in size and complexity, concern arose about the possibility of a malignant glioma. Upon craniotomy, it proved to be a giant cerebral cavernous malformation. This case is remarkable in that most cavernous malformations do not become symptomatic before the third decade of life and rarely attain such a large size.


A 15-year-old white boy was in his usual excellent health until May 1999, when he began to experience severe left-sided headaches accompanied by nausea and vomiting. When the headaches did not respond to antimigraine therapy, he underwent magnetic resonance imaging (MRI) that showed a well-circumscribed, round, left-sided 4 x 5 cm-diameter parieto-occipital region mass containing blood and blood products (Fig. 1). Neurologic and ophthalmologic examinations revealed no abnormalities except for an incomplete right homonymous hemianopia (Fig. 2). A cerebral angiogram showed evidence of a solid mass without any vascular abnormalities. As the mass was considered probably benign, no intervention took place.

In June 2001, 21 months later, the patient had a tonic-clonic seizure followed by loss of consciousness for 30 minutes. A computed tomographic (CT) scan and repeat MRI showed that the hemorrhagic mass had increased in size to 7 x 5 cm (Fig. 3). Neurologic and ocular examinations revealed no new abnormalities; the right homonymous field defect had improved. Because of its large size and apparent growth, the lesion was suspected of being a glial malignancy, and a left occipital craniotomy was performed.
FIG. 2. Static perimetry at initial presentation (Humphrey 24-2) shows an incomplete right homonymous hemianopia.

During surgery, a large, well-circumscribed, multi-lobulated encapsulated lesion was encountered that contained multiple lobules filled with blood and blood products of different ages. It was completely resected.

Histopathologic examination revealed tortuous and disorganized vascular channels containing thrombi of varying ages. The vessels were separated by fibrotic tissue containing foci of calcification and hemosiderin deposition (Fig. 4). These findings were consistent with a cerebral cavernous malformation (CCM).

After surgery, the patient had no new neurologic deficits, although his visual field defect had worsened, becoming a dense right superior homonymous quadrant anopia. MRI performed 2 months after surgery showed only postsurgical changes in the left-temporo-occipital region.

Cerebral cavernous malformations consist of blood-filled cavities lined by a single layer of endothelium and separated by neuroglia but not neural tissue (1). Calcification and areas of hemorrhage are commonly present within the lesions (1,2). CCMs are usually intraparenchymal, but extraparenchymal lesions are well described, particularly in the region of the cavernous sinus (3-5). Although most are sporadic occurrences, some are transmitted as an autosomal-dominant trait (3). Most lesions are solitary, but multiple lesions may be present, particularly in hereditary cases.

Cerebral cavernous malformations vary in size from a few millimeters to a few centimeters in diameter. Russell and Rubinstein (1) indicated that the largest CCM was 4 × 3 × 2 cm. Our patient had a CCM that was substantially larger, measuring 5 × 7 cm. Although such cases have been reported, they are quite rare. The mechanism by which such lesions enlarge is recurrent bleeding, followed by organization of the clot, pseudocapsule formation, and secondary expansion. We presume that recurrent hemorrhage produced both the enlargement and the multicystic appearance in our case.

From 30 to 70% of patients with CCMs experience seizures as the first sign of the lesion (3). Others develop slowly progressive neurologic symptoms and signs from...
FIG. 4. Histopathologic of the cavernous malformation (A: low-power view; B: high-power view) shows tortuous and disorganized vascular channels containing thrombi of varying ages. The vessels are separated by fibrotic tissue containing foci of calcification and hemosiderin deposition.

compensation, or acute neurologic deterioration from intraparenchymal or subarachnoid hemorrhage.

The neuroimaging appearance of a CCM is often diagnostic. On noncontrast CT, the lesion is typically round and well-circumscribed, with a homogeneous appearance that is isodense to moderately hyperdense with respect to brain parenchyma. There may be changes consistent with calcification, hemorrhage, or both. Enhancement after intravenous injection of iodinated contrast material varies from absent to striking. MRI typically reveals a low-signal hemosiderin rim that completely surrounds the lesion and is particularly prominent on T2 and gradient-echo images. The center of the lesion typically shows a well-delineated reticulated core of mixed-signal intensities caused by different stages of evolution of repeated hemorrhage. Because of their exquisite sensitivity to blood products, gradient-echo sequences are particularly good at detecting small hemorrhagic lesions. Patients thought to harbor a solitary CCM often are found to have multiple lesions by this technique (1,3–5). Angiography is typically of little value in assessing CCMs, which show no vascular blush and no feeding arteries or draining veins.

The differential diagnosis of a CCM includes a low-grade or malignant cystic glioma, a primitive neuroectodermal tumor (PNET), a thrombosed arteriovenous malformation, and an intracerebral hematoma. In many instances, as in our case, the correct diagnosis is not apparent until histopathologic examination of the specimen is made.

The treatment of symptomatic CCMs is controversial. Because of the low likelihood of hemorrhage or growth, most authors recommend observation for patients who are asymptomatic or for those who present only with seizures, particularly if the lesions lie in eloquent brain regions (6). Surgical excision is the treatment of choice for symptomatic CCMs located in accessible, noneloquent cerebral or cerebellar regions (7). Stereotactic radiosurgery is increasingly recommended for the less accessible, deep cerebral, and brainstem lesions (8). Our patient underwent excision of the lesion with an excellent functional result.

REFERENCES
Self-inflicted Blindness and Brown-Séquard Syndrome

Tim L. Gray, MBBS, Arthur Karagiannis, FRACO, John L. Crompton, FRACO, and Dinesh Selva, FRACO

Abstract: A 30-year-old paranoid schizophrenic man suffered a psychotic episode while flying on an airplane, locked himself in the bathroom, detached the temples of his sunglasses, and stabbed them deeply into both medial orbits. He then secured one temple into the door hinge and rammed the back of his neck repeatedly against it. The injuries caused no light perception from optic nerve trauma and a Brown-Séquard hemitransection of the spinal cord.

An 30-year-old Canadian man had a paranoid psychotic episode while flying from Canada to Melbourne, Australia. He became convinced that the cabin staff was plotting to kill him and decided to commit suicide. While

locked in the airplane’s bathroom, he removed the temples of his sunglasses, stabbed them deeply into both medial orbits and then jammed one of the temples into the hinge of the restroom door. He proceeded to hit the back of his neck against the temple, piercing his spine, and fell to the ground, partially paralyzed.

On presentation to our medical facility, he complained of blindness and left-sided weakness. Examination revealed no light perception in both eyes with dilated, non-reactive pupils. There were bilateral periorcular hematomas, puncture wounds at both caruncles and a small right medial conjunctival laceration. Extraocular movements were intact on the left but a complete ophthalmoplegia was present on the right. Examination of the fundi was unremarkable. Neurological testing revealed a left hemiparesis and ipsilateral loss of vibration and position sense. On the right side of his body, caudal to the fourth cervical spinal segment (C-4), he had reduced temperature and pain sensation [spinothalamic
fibers cross the spinal cord approximately two spinal levels above their point of entry (1). These findings were consistent with a Brown-Séquard (spinal cord hemitranssection) syndrome at C-2.

A cervical x-ray demonstrated the arm of the sunglasses extending into his spinal canal between the first and second cervical spinous processes (Fig. 1). The patient was taken to the operating room for exploration of the wounds. The temple was removed and intravenous methylprednisolone was administered for 48 hours. Magnetic resonance imaging (MRI) confirmed direct injury to both optic nerves at the orbital apices (Fig. 2) and to the cervical spinal cord (Figs. 3, 4). Visually evoked potentials (VEPs) were absent for the OD and poorly developed for the left.

Three months later, his vision had improved to hand movements on the left but he remained at hand movements on the right. He now had a full range of extraocular movements bilaterally. His right pupil was nonreactive to light and the left showed a sluggish response. Funduscopic examination demonstrated bilateral optic disc pallor. VEPs confirmed some minor improvement in responses for the OS but responses from the right were still very depressed. There was moderate neurologic recovery from his spinal cord injury so that he was able to walk with a walking frame. Six months after returning to Canada, during a period of noncompliance with antipsychotic medication, he committed suicide by hanging himself.

This case is extraordinary for the devastating injuries inflicted with what would normally be considered an innocuous instrument—a pair of sunglasses. It is, we believe, the first documented case of a combination of self-inflicted bilateral optic nerve damage and Brown-Séquard syndrome.

Brown-Séquard syndrome is named after Charles-Edouard Brown-Séquard (1817-1894), a French physician who worked on both sides of the Atlantic—in New York, Richmond, Boston, and Geneva. He contributed to many fields of medicine, most notably to our understanding of spinal pathway anatomy and physiology. A founding physician at the National Hospital for Nervous Diseases, Queen’s Square, London (2), he later succeeded Claude Bernard in the chair of experimental medicine at the Collège de France in Paris.

The features of Brown-Séquard syndrome, or hemitranssection of the spinal cord, are most often caused by trauma or neoplasm (3). In most cases, the hemitranssection is partial and not all the signs are found. Additional signs not seen in our case include an ipsilateral lower motor neuron paralysis resulting from destruction of the anterior gray column or nerve root, and a band of cutaneous anesthesia resulting from destruction of...

FIG. 3. Sagittal T2 MRI shows high signal of reactive edema around the penetrating injury in the spinal cord (arrow). There is soft tissue edema in the suboccipital path of the wound.

FIG. 4. Axial T2 MRI at the C1–2 level shows a band of low signal extending through the spinal cord (arrow) consistent with the fresh hemorrhage of a penetrating injury.
the posterior root of the spinal nerve at the level of the lesion.

Injury to the optic nerves may have occurred by several mechanisms. Direct trauma to both optic nerves resulting in ischemic neuropathy from disruption of the pial vessels supplying them is the most likely. A subperiosteal hematoma can compress the optic nerve at the canal but was not seen in the MRI (4). An intracanal hematoma or edema could have directly compressed the optic nerve, third, fourth, and sixth cranial nerves and would be the likely cause of the neurapraxia leading to the temporary complete right ophthalmoplegia.

REFERENCES

Pathogenesis of Nonarteritic Anterior Ischemic Optic Neuropathy

Anthony C. Arnold, MD

Abstract: Based on histopathology, electron microscopic corrosion cast studies, optic nerve blood flow studies, and clinical data, the pathogenesis of idiopathic nonarteritic ischemic optic neuropathy includes the following features: (1) structurally crowded optic discs are predisposed; (2) laminar and retrolaminar regions are the most common locations for infarction; (3) there is flow impairment in the prelaminar optic disc during the acute phase; (4) lack of consistent choroidal flow impairment and the retrolaminar location of infarcts suggest vasculopathy within or distal to the paraoptic branches of the posterior choroidal arteries; (5) diabetes is the most consistently identified vasculopathic risk factor; (6) impaired autoregulation of the disc circulation by atherosclerosis, with a possible contribution from serotonin and endothelin-mediated vasospasm, may play a role; and (7) progression may be caused by secondary cell death after the initial ischemic insult or compression from cavernous degeneration and mechanical axonal distortion.


Nonarteritic anterior ischemic optic neuropathy (NAION) is presumed to result from circulatory insufficiency within the optic nerve head, but the specific mechanism and location of the vasculopathy remain unproven. In the arteritic form of AION (AAION), by contrast, histopathologic evidence confirms both inflammatory occlusion of short posterior ciliary arteries (SPCAs) and infarction within the optic nerve head. Much of the research regarding the etiology of NAION has centered on the SPCA and choroidal circulations and factors that might compromise them. Studies have included anatomic and physiologic (blood flow) analysis of the optic discs in NAION, along with attempts to link various vascular risk factors to affected subject populations. Several authorities have recently speculated as to the relative contributions of these interrelated elements (1-5). This review summarizes evidence for the roles of the following factors in the pathogenesis of idiopathic NAION, the form that is not associated with specific precipitating factors such as acute systemic hypotension or anemia: (1) Optic disc vasculopathy and infarction: histopathology and electron microscopic corrosion casting studies of optic disc circulation; (2) optic disc blood flow impairment: studies of optic nerve head and peripapillary choroidal blood flow, including fluorescein angiography, indocyanine green angiography (ICG), color Doppler flow (CDF) studies, and laser Doppler flow (LDF) studies; (3) risk factors for vascular occlusion: prevalence studies of vasculopathic and prothrombotic risk factors; and (4) other contributing factors: optic disc structure "crowding," systemic nocturnal hypotension, vasospasm, impaired autoregulation, and secondary neuronal degeneration mechanisms.

HISTOPATHOLOGY

What is the histopathologic evidence that there is occlusive vasculopathy within the optic disc microcirculation in NAION and that the optic nerve damage is truly ischemic?

In AAION, there is extensive histopathologic documentation of infarction in the paralaminar regions of the optic nerve head and inflammation, thrombosis, and occlusion within the SPCAs (6-9). While these findings confirm that SPCA occlusion can and does produce optic disc infarction, the corresponding evidence that this takes place in NAION is lacking. Six cases of nonarteritic optic nerve head infarction have been reported, three of which were atypical cases, including internal carotid occlusion, multiple embolic lesions, and severe acute blood loss, rather than classic idiopathic NAION (10-14). The SPCAs were described only in a case in which emboli within these vessels produced optic disc infarction, and in which the central retinal and pial arteries were also filled with emboli. In other words, this was not a standard case of NAION. No confirmation of lipohyalinosis or other occlusive process within the disc vascular supply has been documented in these or other cases. In a series of 193 eyes collected over 47 years with a histopathologic diagnosis of ischemic optic neuropathy, Knox et al (15) documented infarction, but

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FIG. 1. Photomicrograph of optic nerve with ischemic optic neuropathy and cavernous degeneration. The large cavern is located predominantly in the retrolaminar optic nerve and produces severe leftward displacement of the adjacent intact axons. (Alcian blue, original magnification ×30). Reprinted with permission (15).

clinical data are largely unreported, and the cases with classic idiopathic NAION are difficult to distinguish. In this series, as in the other cases, the location of vascular compromise is undocumented.

Two features are evident from histopathologic studies of both AAION and NAION (Fig. 1): (1) Infarction is primarily located in the retrolaminar region of the optic nerve head, with occasional extension to the lamina and prelaminar layers. This pattern speaks against a primary role for the choroidal circulation in pathogenesis. Although the proportion of the optic disc vasculature supplied by the peripapillary choroid has been controversial, researchers agree that the choroidal contribution is primarily to the prelaminar, not laminar or postlaminar layers. Infarction originating more posteriorly implicates the SPCA branches directly supplying the optic disc. (2) Many cases of NAION (36% in Knox’s series) have shown evidence of cavernous degeneration, with displacement and distortion of adjacent axons (in some cases dramatically) by an expanded mucopolysaccharide deposit. This finding raises the question of focal secondary compression as a contributing feature in the progressive form of NAION. Unfortunately, correlation of this finding with clinical evidence of progression is lacking.

ELECTRON MICROSCOPIC CORROSION CAST STUDIES

What is the electron microscopic evidence that there is occlusive vasculopathy within the optic disc microcirculation?

Olver et al (16) and Onda et al (17) have demonstrated in autopsy eyes that the optic disc is supplied by a partial or complete vascular circle (corresponding to prior descriptions of the circle of Zinn-Haller) derived from the SPCAs, and that this vascular circle may have distinct upper and lower halves consistent with the altitudinal damage of the nerve head commonly seen in NAION (Fig. 2). These studies also demonstrate the separation of the paraoptic branches of the SPCAs (which supply the optic nerve head) from the choroidal branches. Unfortunately, no such studies at this level of the circulation in cases of NAION have been performed.

OPTIC NERVE HEAD BLOOD FLOW STUDIES

What is the evidence that there is decreased blood flow within the optic nerve head in NAION?

Fluorescein Angiography

Fluorescein angiographic studies in AAION consistently show severely impaired filling of the optic disc and the choroid, in the peripapillary region and diffusely (18–21). In NAION, studies show similarly delayed filling of the prelaminar optic disc (deeper layers are not well visualized) in the edematous phase, prior to the development of the impaired filling that eventually comes with any form of atrophy (due to loss of supporting vasculature). This is the most compelling in vivo evidence of optic disc circulatory impairment in NAION (18–20). In studies by Arnold et al (22,23), delayed prelaminar optic disc filling (>5 seconds

FIG. 2. Scanning electron photomicrograph of the vasculature of the posterior globe. Superior (long solid arrow) and inferior (long empty arrow) anastomoses from the medial (short solid arrow) and lateral (short empty arrow) short posterior ciliary arteries (SPCAs) suggest a possible anatomic correlation for the altitudinal pattern of optic nerve damage often seen in NAION. Reprinted with permission (16).
Whether the optic disc in NAION lies within a watershed zone between territories supplied by the PCA branches is a controversial issue (4,5,22,29,30). Hayreh (29,30) has suggested that the “watershed concept” is a major factor in the development of optic nerve ischemia, noting its presence in a substantial number of NAION patients studied with fluorescein angiography and indicating that impaired perfusion pressure within the distribution of a PCA predisposes the optic disc to infarction. In the study of Arnold and Hepler (22), however, significantly delayed filling (>5 seconds) of a vertical watershed zone encompassing at least a quadrant of the optic disc was recorded more often in 43 normal subjects (42%) than among 41 (27%) patients with NAION (p = 0.15). Filling of the disc located within these zones, either in normal subjects or in NAION, did not correlate with adjacent choroidal filling, again consistent with a separate source of flow to the optic disc (the paraoptic branches of the SPCAs). The lack of correlation of disc and choroidal filling would militate against watershed ischemia as a cause of NAION, as disc and parapapillary choroidal flow would be expected to slow together. Moreover, the choriocapillaris, which is the layer visualized on fluorescein angiography and whose absence is interpreted as a watershed zone, does not materially contribute to the laminar region optic disc vascular supply. While the location of the optic disc at the limit of the distribution of a PCA may predispose it to ischemic damage if there is significantly decreased PCA flow, as evidenced by the delayed flow in the PCA and choroid seen in some cases, this is not consistently documented. Fluorescein angiographic findings are more consistent with impaired flow in the direct paraoptic branches to the disc rather than a watershed phenomenon.

Later than choroid and retinal vasculature) was noted in 76% of subjects with acute NAION, compared with no delay in normal controls or in subjects with nonischemic optic disc edema (Fig. 3). This suggests that the delayed filling is a primary process rather than one secondary to disc edema. In these studies, (22,23) the overlying disc surface vasculature, derived from the retinal arterial circulation, showed variable filling patterns: in some cases substantially impaired and in other cases prominently dilated with early filling that precluded evaluation of the filling pattern of the underlying of the disc in NAION (1,22,24).

Arnold and Hepler (22) and Siatkowski et al (21) have found that segmental parapapillary choroidal filling delay (>5 seconds) is not a consistent feature in NAION (it occurred in only 46% of NAION cases, and similar segmental delays were commonly seen in normal subjects [58%]). Furthermore, segments of optic disc and adjacent choroidal filling were poorly correlated. Optic disc filling delay—segmental or complete—was seen adjacent to normally filling choroidal segments, and vice versa (Fig. 3A). Similar findings have been reported with indocyanine green (ICG) studies of the choroidal circulation, which show substantial slowing in AAION but not in NAION (25–28). These data suggest that in NAION, the level of vascular occlusion lies within the distribution of the paraoptic branches of the SPCAs, after their take-off from the choroidal branches.

FIG. 3. A: Fluorescein angiography in NAION. Filling of the optic disc is delayed, but the peripapillary choroid fills normally, suggesting impaired perfusion within the paraoptic branches of the short posterior ciliary arteries (SPCAs) supplying the optic disc distal to the branching of the choroidal vessels from the SPCAs. B: Fluorescein angiography in nonischemic optic disc edema (papillitis) shows normal filling of the disc, without filling delay, followed by late hyperfluorescence. A: reprinted with permission (22); B: reprinted with permission (23).

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Color Doppler Flow Studies

With current technology, CDF studies have not conclusively localized impaired blood flow in NAION. Flaherty et al (31) measured vascular flow velocities and calculated resistance of the ophthalmic arteries (OA), central retinal arteries (CRA), and SPCA in 25 patients with progressive NAION undergoing optic nerve sheath decompression surgery; fellow eyes were used as controls. Preoperatively, both CRA and SPCA velocities were lower in NAION than in control eyes; postoperatively, an increase in velocity was noted in OA and CRA, and a decrease in calculated resistance was found in the SPCA. While this was interpreted as showing initial flow impairment in NAION, which improved after surgery, the study was widely criticized (32). CDF studies of the SPCA parameters have been controversial because:

1. The technique measures flow velocities rather than volume; increase in velocity may actually indicate a decrease in blood flow due to stenosis; flow volume itself cannot be measured accurately because the diameter of the specific vessels measured is not known;
2. Calculations of vascular resistance may be inaccurate if assumptions regarding the autoregulatory characteristics of the vascular bed tested are invalid;
3. Measuring the OA and SPCA flow parameters in the orbit may not represent flow parameters within the paraoptic branches, which supply optic disc; and
4. Measuring the CRA flow parameters is unrelated to the vascular supply of laminar regions of the optic disc.

Laser Doppler Flow Studies

Laser Doppler flow studies have also not conclusively documented or localized relevant circulating impairment in NAION. Stationary (laser Doppler flowmetry, or LDF) or scanning (Heidelberg Retinal Flowmeter, or HRF) laser imaging methods measure surface blood flow derived from the retinal arterial circulation, rather than flow derived from the SPCAs, which supply the deeper layers of the optic disc involved in NAION. Measurements by HRF are limited to 300- to 400-μm depth. Newer LDF techniques may reach depths of up to 1000 μm, which might include a component of SPCA-derived circulation, but specific contributions from various circulatory components is unproven. In evaluating LDF measurements of optic disc blood flow in rhesus monkey eyes after manipulation of ciliary and retinal circulations, Petrig et al (33) found that flow measurements were decreased with occlusion of the CRA, but not the PCAs.

These techniques have been used extensively in the study of glaucoma, but they have not been widely applied in NAION. Such measurements are confounded by the disc edema and congestion found in this disorder, in many cases resulting in increased surface vascularity, occasionally profoundly so (luxury disc perfusion) (22,24). However, Leiba et al (34) reported that optic nerve head blood flow, as measured by HRF, was diminished in NAION compared with fellow eyes (n = 14), and in affected and fellow eyes compared with age-matched controls (n = 7). This study was limited by small numbers of subjects, time delay after onset to study (up to 6 months), and lack of control for optic disc structure (cup-disc ratio), which could have a substantial effect on measured surface vasculature, in addition to the issues of the depth of the circulatory bed measured by the technique.

Carotid Stenosis: Duplex Studies

Carotid stenosis has not been shown to be associated with NAION. Fry et al (35) performed carotid Duplex scans in 15 patients with NAION, in 11 patients with transient monococular blindness (TMB), and in 30 age-matched control subjects. Mean stenosis was not significantly worse in NAION patients (19%) than in controls (9%), but much worse in those with TMB (77%). Two of 15 patients with NAION had stenosis greater than 30%, compared with 5 of 30 controls and 10 of 11 patients with TMB. Muller et al (36) did not find hemodynamically significant stenosis in any of 17 subjects with NAION.

RISK FACTORS FOR OCCLUSIVE VASCULOPATHY

What is the evidence that risk factors for vascular occlusion are associated with NAION?

Several cross-sectional case series have estimated the prevalence of systemic diseases that might predispose to vasculopathy in patients with NAION (37-41). Systemic hypertension has been documented in 34 to 47% of patients. However, in those studies that compared these figures to matched population data from the National Health Survey, statistical significance was reached only in the younger age group, those aged between 45 and 64 years. In contrast, Hayreh et al (40), found a significantly increased prevalence of vascular risk factors in all age groups. Diabetes has been reported in 10 to 24% of NAION cases, with significantly increased prevalence at all ages in all but one study. Diabetes has also been associated with the development of NAION at a younger age in most series. In these studies, the association of NAION with other cardiovascular events such as stroke and myocardial infarction has been inconsistent.

In a case-control study of NAION, Jacobson et al (42) addressed these and the additional risk factors of smoking and hypercholesterolemia in 51 patients compared with two separate control groups. While hypertension was found in 57% of patients, it was not found to be significantly more
prevalent than among controls in any age group. Diabetes, found in 34%, was a significant risk factor in all age groups. Neither hypercholesterolemia nor smoking demonstrated significant risk. The 61-patient case control study of Salomon et al (43) also confirmed diabetes but not hypertension as a risk factor. Additionally, hypercholesterolemia was found to be a significant risk factor, while smoking was not. In two other case-control studies, (44,45) hyperlipidemia and smoking were both identified as risk factors. A large (137 cases) but uncontrolled study by Chung et al (46) concluded that smoking was a significant risk factor on the basis that smokers developed NAION at a significantly younger age than nonsmokers.

The relation between NAION and elevated plasma homocysteine levels remains uncertain. Kawasaki et al (47) reported 2/17 NAION cases younger than age 50 with elevated homocysteine, while Bisou et al (48) reported normal values in 14/14 NAION cases with a mean age of 43 years. Pianka et al (49) reported elevated levels in 45% of 40 NAION patients (mean age 66 years) but in only 9.8% of control subjects. Weger et al (50) also reported significant elevation in 59 NAION patients compared with control subjects.

Isolated reports (51,52) have documented prothrombotic risk factors in patients with NAION. But a large study by Salomon et al (43) to evaluate lupus anticoagulant, anticardiolipin antibodies, prothrombotic polymorphisms, and deficiencies of protein C, S, and antithrombin III in a series of 61 patients with NAION and 90 control subjects failed to find any association of these factors with NAION.

OTHER FACTORS

What is the evidence for other pathogenetic factors in NAION?

Mechanical Factors

Optic disc structural features play an unknown role in AION. The discs in AAION are normal in diameter and cup size (53). Those in NAION are most often small in diameter, with small or absent cups, suggesting to many investigators that "crowding" plays a role in pathogenesis, although exactly how it might do so is unclear (54–58). Possibilities include:

1. Crowding produces intracellular axonal swelling secondary to mechanical obstruction to axoplasmic flow, particularly at the most crowded region, the cribriform plate;
2. Subclinical ischemia due to lipolysis and/or other factors produces additional axoplasmic stasis, with swelling causing compression and further compromise of the microcirculation in the crowded laminar region;
3. Crowding of the disc is associated with an abnormally stiff (less compliant) cribriform plate region, exaggerating factors 1 and 2; and
4. After acute ischemia, secondary obstruction to axoplasmic flow occurs, with decreased return of neurotrophins, and resultant additional ganglion cell death.

Studies of the microstructure and ultrastructure of the optic disc in glaucoma suggest that structural aspects of the laminar region may contribute to pathogenesis. Such factors as poor support of axons, or increased shear forces applied to them by the cribriform plate in response to mechanical deformation from elevated intraocular pressure (due to pore size, collagen content, or abnormal compliance) have been implicated. Similar studies have not been performed in eyes with NAION.

Nocturnal Hypotension

Hayreh et al (59) has proposed that nocturnal systemic hypotension may play a role in the development of NAION, stating that the relative hypotension that normally occurs with sleep may chronically compromise optic disc circulation, particularly in those patients with an exaggerated nocturnal "dip" in blood pressure or in patients, such as those with systemic hypertension, where optic disc circulation autoregulatory mechanisms are impaired (59). This effect might be worsened with aggressive antihypertensive therapy, particularly if administered at night, by further exacerbating the nocturnal dip. Hayreh et al (59) performed 24-hour ambulatory blood pressure monitoring in 52 cases of NAION compared with 19 cases of primary open angle glaucoma (POAG) and 65 cases of normal tension glaucoma (NTG). Mean decrease in systolic and diastolic blood pressure of 25.3% and 31.2%, respectively, were noted in NAION. In general, no significant differences in blood pressure decrease were observed between NAION, NTG, and POAG; however, the 31.2% diastolic decrease in NAION was significantly less (p = 0.004) than the 36.0% figure for NTG. No control subjects were monitored, but the figures for an age-matched normal population range from 7 to 21%. In patients with NAION and systemic hypertension on medication, nighttime blood pressure figures were significantly lower in those with visual field deterioration. From these data, the authors implied that nocturnal systemic hypotension plays a significant role in the development of NAION in certain susceptible subjects. They subsequently (60) reported similar conclusions based on data from 114 NAION, 131 NTG, and 30 POAG subjects, including some patients from the original study (59).

Landau et al (61) performed 24-hour ambulatory blood pressure monitoring in 24 subjects with NAION that was controlled with 24 age-matched, other disease-matched, and medication-matched subjects. Mean decreases of 11% systolic and 18% diastolic were measured.
in NAION, compared with 13% and 18% respectively in controls, showing no significant difference. They did, however, see mildly lower mean daytime blood pressures in NAION than in controls, averaging 5 to 7 mm Hg. The largest difference was noted in the morning, indicating a slower morning rise in pressure in NAION subjects when compared with normal control subjects.

The contradictory results regarding level of nocturnal "dip" in NAION and whether chronic or intermittent low systemic blood pressure is a factor in etiology remain unresolved. A lively exchange between the authors of the two studies was published in 1997 (62,63).

Vasospasm and Impaired Autoregulation
Whatever the cause for impaired blood flow in the optic nerve vasculature, persistent hypoperfusion may require impairment in the normal autoregulatory mechanisms of the optic nerve head. Flow is normally maintained constant with variations in perfusion pressure, intraocular pressure, and metabolic conditions (including tissue oxygen and CO2 levels) by factors that vary resistance to flow. Autonomic input to vessels and vasoactive substances (including vasoconstrictor endothelins and vasodilator nitric oxide) released in response to metabolic influences or mechanical deformation of vascular smooth muscle contribute to the regulation of blood flow in response to these external influences. These autoregulatory mechanisms may be reduced by arteriosclerosis, vasospasm, or antihypertensive medications, including beta-blockers.

Hayreh (64,65) has postulated that endogenous serotonin, released during platelet aggregation into atherosclerotic plaques, may play a role in the development of ischemic optic nerve damage via its role in vasoconstriction of arterioles and resultant impaired autoregulation, possibly mediated by endothelial-derived vasoactive agents such as endothelins. He has reported serotonin-induced vasoconstriction in CRA and PCAs in atherosclerotic monkeys that is reversed by discontinuing an atherogenic diet.

The role of endothelins in optic disc ischemia is under intensive study, particularly as endothelin-derived vasoconstrictor of endothelins and resultant impaired autoregulation, possibly mediated by endothelial-derived vasoactive agents such as endothelins. He has reported serotonin-induced vasoconstriction in CRA and PCAs in atherosclerotic monkeys that is reversed by discontinuing an atherogenic diet.

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Celular Mechanisms
Experimental models of optic nerve ischemia induced by endothelins have been shown to be associated with elevated levels of glutamate in the overlying vitreous (68). Levin et al (69) have shown evidence of apoptosis in the ganglion cells in a case of NAION. Thus, ischemia-induced cell death may result in release of glutamate, with further cell damage and death by excitotoxic induction of apoptosis. The issue of secondary neuronal damage after ischemic injury by this and other cellular mechanisms, including free radical production and lipid peroxidation, is currently being studied as a potentially treatable component in the progressive process of NAION (70).

REFERENCES


Editor's Note: This section contains brief reviews of articles that have appeared in other journals within the past six months. From a comprehensive list of clinical and scientific medical journals, each reviewer has selected about 30 titles and reviewed the most pertinent articles. The March and September issues include reviews from ophthalmology and medicine journals; the June and December issues include reviews from neuroclinical and neuroscience journals.

Neuroscience Journals

Reviewer: Syndee Givre, MD, PhD
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I. Neurogenesis in the Adult Brain


The Journal of Neuroscience, Volume 22, Number 3, contains a review on neurogenesis in the adult mammalian brain, including a fine introduction by Fred H. Gage and several authoritative papers.

Although neurogenesis is common in many adult vertebrates, neuroscience dogma has it that no new neurons are added to the mammalian CNS in adulthood. This dogma stemmed from early histologic studies showing a scarcity of mitotic figures and intermediate cell forms, from simple to more complex neurons, in adult brains. Furthermore, the intricacy of dendritic and axonal branching of neurons and the complexity of their interconnections made it difficult to conceive of how new neurons could functionally integrate into the mature brain. But about 40 years ago, evidence of new neurons in the adult brain began to accrue. After much initial skepticism, neurogenesis in adult mammals, including primates, is now accepted as fact. It occurs in the subventricular zone adjacent to the olfactory bulb and in the dentate gyrus; it may occur in other regions of the brain as well. Some of the papers from this review are summarized below.


This is an important review for those who wish to read original work on neurogenesis with an appropriately critical eye. The author outlines the common techniques used for demonstrating new neurons. The oldest method involves intraventricular injection of $^3$H-thymidine, which competes with endogenous thymidine for uptake by cells undergoing nuclear DNA synthesis in preparation for mitosis. $^3$H-thymidine is detected by autoradiography. More recently, another thymidine analogue, bromodeoxyuridine (BrdU) has been used. The advantage of BrdU is that it is detected immunohistochemically and can be used in double labeling experiments with other immunohistochemical markers that are specific for neurons. The pitfalls of each technique, mainly those resulting in false labeling, are discussed in detail. Rakic proposes stringent criteria for asserting neurogenesis, including the demonstration of mitotic figures, unambiguous identification of new cells as neurons and precise definition of the term "adult."


The authors review techniques used to demonstrate neurogenesis and their pitfalls. They also discuss other factors that can affect the number and survival rate of new neurons. Studies have shown that learning tasks, housing in enriched or natural environment settings, and ovarian steroids can enhance the proliferation and survival of new neurons in the hippocampus. Stress (predator odor exposure in adult rats, for example) reduces new neuron proliferation in the dentate gyrus. Glucocorticoids (released in stressful situations) produce a similar inhibition in the absence of stress. The authors conclude with a discussion of the possible role of new neurons in the adult brain. Because new neurons are so few in number, the authors speculate that these neurons would have to possess special properties to have any functional impact relative to mature neurons.


The author and his colleagues are responsible for pioneering work in elucidating the production and replacement of neurons in the adult avian brain. The avian system is an important model for adult mammalian neurogenesis. In adult birds, neurogenesis is relatively common but occurs only in restricted brain regions and only for certain neuronal types and therefore affects a small minority of cells. In songbirds, the spontaneous loss of neurons and neurogenesis occur continuously in the high vocal center (HVC), a part of the cortex, such that the absolute number of neurons in HVC is constant. HVC controls song, a seasonal behavior. Changes in the light/dark period lead to changes in testosterone levels and higher testosterone levels promote...
singing. Testosterone and singing additively promote the survival of new HVC neurons via a rise in brain-derived neurotrophic factor. If singing is discouraged, many of the new neurons in HVC disappear.

The author concludes with a strong argument for studying adult neurogenesis in free-ranging animals leading relatively normal lives (as has been done in birds). This may maximize our chance of observing what is likely an uncommon feature of brain functioning in mammals.


The authors studied the effect of deafening and denervation of the vocal organ of songbirds on adult neurogenesis as measured by BrdU labeling. Experimental groups consisted of deafened birds, unilaterally denervated birds (able to hear and imitate song), bilaterally denervated birds (able to hear but not imitate song), and deafened plus unilaterally denervated birds (able to sing, but not hear and imitate song).

The results showed that the absolute number of HVC neurons was no different in any experimental group compared with controls. Neither deafening nor bilateral denervation resulted in a significant change in the number of labeled (new) neurons in HVC. In contrast, unilateral denervation nearly doubled the number of labeled neurons in the contralateral HVC 30 days after BrdU injection. This effect disappeared by 90 days after injection and was not seen if unilateral denervation was combined with deafening.

These data suggest that, in the absence of learning of song (in deafened and bilaterally denervated birds), there is continual and probably preprogrammed culling and replacement of neurons. With song learning (normal birds), culling and replacement may be more selective and, as evidenced by the unilaterally denervated birds, may be based on activity in the particular circuits used to learn.


The authors summarize recent work on the origin of new neurons in the adult subventricular zone (SVZ), the mechanism of migration of these cells, and their potential functions. The subventricular zone lies along the lateral walls of the lateral ventricles. From there, new neurons migrate to the olfactory bulb, where they become mature interneurons. Regarding the origin of new neurons, work from several studies has surprisingly suggested that the neuronal precursor cell in the SVZ may be an astrocyte. In one experiment, SVZ astrocytes were labeled with a retrovirus. Later, labeled neurons were found integrated into the olfactory bulb.

In adult rodents, new neurons must migrate from the SVZ to the olfactory bulb several millimeters away. These new neurons, with growth cones on their leading edges, move along each other in chains that are ensheathed by astrocytes. This phenomenon occurs in the absence of the olfactory bulb, implying that migration is not simply a response to a chemotactic molecule secreted by this structure. Once the new neurons reach the edge of the olfactory bulb, they separate from the chain and individually move farther into the tissue, where a fraction differentiates into granule neurons. The recruitment of new neurons to the olfactory bulb is inhibited by naris closure. The authors propose that new neurons in the olfactory bulb participate in plasticity and learning and may improve olfactory discrimination. Similar proposals regarding learning and plasticity have been made about the function of new neurons in the mammalian adult hippocampus and the avian song nuclei.


In birds, studies have shown functional links between adult neurogenesis and specific behaviors, song learning being one example. In the hippocampus of adult mammals, similar neurogenesis occurs but its functional implications are less well understood.

The author reviewed studies investigating the possible functions of neurogenesis in adult mammalian hippocampus. The function of the hippocampus itself is poorly understood but is thought to be related to learning and memory. Environmental enrichment, physical activity, and learning a task that relies on hippocampal functioning up-regulate adult hippocampal neurogenesis. Conversely, changes in the rate of neurogenesis and the survival of new neurons have been shown to affect subsequent learning of hippocampus-mediated behaviors. Mice that have received a cytostatic agent to inhibit neurogenesis perform worse on a hippocampus-dependent task. The author proposes that adult hippocampal neurogenesis enables this structure to continuously deal with novel and increasingly complex stimuli.

The mere existence of neurogenesis in adult mammals has generated many important questions posed in this review. Given that mammals have a multitude of cell types that divide throughout life, why is it that most neurons in mammals do not replicate? Adult insects, fish, and amphibians can replicate neurons; why are there species-specific variations in this phenomenon? Furthermore, why is there variation in the degree of neurogenesis amongst different brain regions? What implications, if any, does this variation
have with regard to the function of adult neurogenesis? Which cells are giving rise to the new neurons? Most importantly, for clinical purposes, can the phenomenon of neurogenesis be harnessed to reinstate brain function that has been lost by disease or other damage?

II. Dyslexia


Dyslexia, characterized by reading difficulty in those who otherwise have normal intelligence, schooling, and motivation, affects 5% to 17% of people. The author reviews neuroimaging data that support a view of dyslexia as a problem of phonological and rapid auditory processing.

Multiple positron emission tomography experiments have reported a reduction or absence of activity in the left temporoparietal cortex in dyslexic adults performing phonological processing of visually presented material. In one task, for example, subjects were asked to determine if a visually presented letter rhymed with the letter "B." The finding of similar results in functional magnetic resonance imaging (fMRI) and magnetoencephalographic (MEG) studies in children implies that, rather than being a marker for compensation for dyslexia in adults, reduced activity in temporoparietal cortex reflects the fundamental dysfunction in dyslexia. Reduced temporoparietal activity has also been found in dyslexic men from the United Kingdom, Italy, and France.

The processing of rapid auditory stimuli is evaluated in tasks in which nonlinguistic stimuli designed to mimic the rapid temporal changes of speech syllables are presented. Both event-related potential (ERP) and MEG studies have demonstrated abnormal brain processing of rapid auditory stimuli in dyslexics. Functional MRI studies have shown reduced activity in the left prefrontal cortex of dyslexics hearing rapidly presented auditory stimuli. Three dyslexic subjects underwent training to improve rapid auditory processing. After training, two of these subjects had significant improvement in rapid auditory processing tests, and these subjects had significantly increased activity in the left prefrontal cortex on fMRI compared with their pretraining scans. The third subject failed to improve behaviorally on fMRI.

These electrophysiologic and neuro-imaging experiments provide evidence that dyslexia is a dysfunction of auditory phonological processing. Having a better understanding of the fundamental dysfunction in dyslexia will ultimately lead to better treatment strategies and possibly prevention. Furthermore, the results of these studies can be passed on to patients, many of whom believe dyslexia to be a visual problem.

III. Visual Perception


Blindsight refers to the presence of residual visual abilities in areas of scotoma induced by damage to primary visual cortex. The existence of blindsight is not universally accepted; those who doubt its existence generally believe that residual vision results from incomplete damage to primary visual cortex. Proponents of blindsight believe that visual pathways not involving primary visual cortex, such as those involving the superior colliculus, pulvinar, and extrastriate cortex, mediate residual vision.

In order to further investigate the mechanism of blindsight, an adult hemianope was asked to perform a divided attention task. The 41-year-old subject had had head trauma at age 8, leaving him with a right homonymous hemianopia and 3.5 degrees of macular sparing. With central fixation maintained, stimuli were presented individually either in the blind or sighted hemifield or simultaneously in both hemifields outside of the spared area, at 10 degrees eccentricity. Blank trials with no target also occurred. The subject was instructed to indicate whether targets were detected in the seeing field, the blind field, both fields, or not at all. In normal subjects, it is well known that divided attention to multiple visual targets decreases performance in target detection tasks.

For individually presented targets, accuracy of detection in the intact hemifield was perfect and accuracy of detection in the blind hemifield was significantly above chance. Simultaneous presentation of targets in the intact and blind hemifields dramatically and significantly increased the detection of targets in the blind hemifield. This effect was significantly increased when the target in the intact hemifield was in the same location with respect to the vertical meridian (upper field, on the horizontal meridian or lower field) as the target in the blind hemifield.

Thus, divided attention enhanced target detection in the blind field of this hemianope in contrast to the detrimental effect of divided attention in subjects with bilaterally intact primary visual pathways. This difference between normal subjects and the hemianopic subject suggests that blindsight is not likely to be the result of sparing of the primary visual pathways.


Two spatially segregated, blinking visual stimuli can be presented simultaneously in such a way that an observer
will have two percepts, either of back-and-forth motion or of two stationary, blinking stimuli. Typically, the two percepts rapidly alternate. Previous studies have demonstrated that manipulating neuronal responses in monkey temporal areas MT and MST, known to be important in motion processing, can alter perception of such " bistable" images. In the current study, perception was allowed to alternate freely and brain activity was measured using fMRI in eight human subjects.

Group and single-subject analyses revealed that hMT+, the human motion complex, an area that includes the homologue of monkey MT and associated regions, was the area most consistently activated during times when the stimulus was perceived as moving. Signals within hMT+ were subject to event-related time course analysis. Signal intensity in this region significantly rose after perception switched from stationary blinking to moving, and fell (though this did not reach statistical significance) after perceptual transition from moving to stationary blinking. Thus, activity was associated with perception of motion despite the fact that the physical stimulus never changed.

The authors demonstrated that hMT+ plays a role in the conscious perception of motion in humans. Other recent fMRI studies have stressed the importance of activation of visual areas of higher order than MT in initiating switches of perception. However, no such higher-order areas were consistently activated in the current study. The authors propose that, at least for the task they studied, activation of hMT+ alone may be sufficient for the perception of motion.


According to most models, processing of visual information within either the dorsal (motion) pathway or ventral (form) pathway is serial. From V1, information is sent to increasingly complex visual areas and, at some point upstream of V1, perception is achieved. This review article summarizes several lines of data that support the concept that primary visual cortex plays an important role in visual perception.

The first type of evidence comes from experiments measuring response latencies in various visual areas. Strictly serial processing would predict that response latencies are greater in higher-order visual regions. Although this holds true for the earliest responses in V1 versus the earliest responses in upstream areas of the form pathway, the scatter of onset latencies in the form pathway would allow for some neurons in higher-order areas to be activated simultaneously with neurons in V1. In the motion pathway, the earliest onset latencies in areas upstream of V1, such as MT, are identical to those in V1.

Second, some properties of primary visual cortex neurons argue for their role in perception. V1 has the highest resolution retinotopic map of any visual area and the magnification factor for V1 corresponds well with known visual acuities at varying eccentricities across the visual field. Thus, primary visual cortex may play a role in the perception of high acuity vision. The activity of some neurons in V1 is related to perception during binocular rivalry. The relative number of these neurons found in V1 is small compared with higher order areas, but the absolute number may be higher as V1 is the largest visual cortical area. Mental imagery is the perception of images without retinal stimulation and is thought to be a higher order visual function. However, mental imagery of gratings has been shown to activate primary visual cortex in PET studies. Furthermore, single neuron recordings from V1 have shown that stimuli lying outside the classic receptive field can influence the response to stimuli within the classic receptive field in an orientation specific manner. Similarly, when a human subject viewing a stimulus is asked to imagine previously viewed flashing stimuli of a specific orientation, contrast threshold for the central stimulus is reduced. Two properties of this modulation in the human, imagined version of the task suggest that it is generated in early visual cortical regions. First, it is highly orientation specific, as arc neurons in V1. Second, the effect is monocular—no reduction in contrast threshold is seen when the flashing stimuli to be memorized and later imagined are presented to one eye but the task is performed with the central stimulus presented to the other eye. Monocular cells are rare outside of V1.

Finally, attention was previously thought to be a function of only higher order visual cortical neurons. It is now clear that attention modulates the responses of V1 neurons. This implies that primary visual cortex plays a greater role in vision than merely the detection and discrimination of visual stimuli.

Taken together, these data support a role for primary visual cortex in certain types of perception, especially perception of features to which V1 neurons are highly tuned.

IV. Demyelination


In an attempt to generate an easily measurable marker of disease activity in multiple sclerosis (MS), the authors looked at antibodies to S-nitrosocysteine (SNO-cysteine), a
product of the reaction of cysteine and nitric oxide (NO). Nitric oxide, which triggers axonal and oligodendrocyte degeneration, is proposed to be a contributor to tissue damage in MS. Since it is volatile, NO cannot be measured directly, but products of its reactions with amino acids can be measured.

Serum antibodies to SNO-cysteine were measured in rats with experimental autoimmune encephalomyelitis (EAE) and in 31 patients with definite MS. Cerebrospinal fluid antibodies to SNO-cysteine were measured in 25 patients with definite MS.

Rats induced with EAE had antibodies to SNO-cysteine that peaked in concentration one week before the onset of clinical symptoms and well before the appearance of anti-myelin basic protein antibodies. Vehicle-injected rats had no anti-SNO-cysteine antibodies. Titers of anti-SNO-cysteine antibodies significantly correlated with the extent of histologic demyelination in the spinal cord. In patients currently in MS relapse, antibody titers directed against SNO-cysteine were significantly elevated as compared with MS patients in remission and normal controls. In two thirds of secondary progressive MS patients studied, anti-SNO-cysteine antibody titers were significantly elevated as compared with controls and MS patients in remission. Antibodies were detected in only one CSF sample from a patient with MS.

The authors concluded that a rise in circulating anti-SNO-cysteine antibodies occurs before the clinical onset of EAE and that these antibodies are elevated in MS patients during relapse and progressive disease. Anti-SNO-cysteine antibodies may be a useful, easily measurable clinical marker of disease activity in MS.


Remyelination becomes less efficient with age. This phenomenon has implications for life-long demyelinating diseases such as MS. CNS remyelination involves recruitment of oligodendrocyte progenitors into the area of damage and subsequent differentiation of these progenitors into remyelinating oligodendrocytes.

The goal of the authors was to determine which part of this process is affected by aging. The recruitment of oligodendrocyte progenitors after toxin-induced demyelination in the caudal cerebellar peduncle of young rats was compared with that of old rats. To assess differentiation, recruitment rates were then compared with the appearance of remyelinating oligodendrocytes.

The absolute number of oligodendrocytes was similar in normal young and old rat caudal cerebellar peduncle. The demyelinating lesion depleted the involved area of oligodendrocytes, oligodendrocyte progenitors, and astrocytes. Oligodendrocyte progenitors appeared in the lesioned area at postlesion day 5 and, at all time points examined, were greater in density in young animals as compared with old animals. In addition, the appearance of markers for remyelinating oligodendrocytes was delayed in older animals as compared with younger animals.

An important implication of these results is that therapeutic strategies aimed at enhancing remyelination in protracted demyelinating diseases such as MS will have to address both recruitment of oligodendrocyte progenitors and differentiation of these cells.

V. Survival and Regeneration of Retinal Ganglion Cells


Transection of the intraorbital portion of the optic nerve leads to degeneration of the retinal ganglion cell population. Both in vivo and in vitro studies have demonstrated positive effects of neuronal activity and neuronal depolarization on axonal development and survival.

The authors of the current study posited that electrical stimulation might improve the survival of axotomized retinal ganglion cells in vivo. To test this hypothesis, fluorescent gold was applied to the superior colliculus to mark retinal ganglion cells. Five days later, intraorbital optic nerve transection was performed. Electrical stimulation of the optic nerve stump with varying current strengths commenced 10 minutes after optic nerve transection and lasted for 2 hours. Seven days later, the retinas were evaluated for survival of retinal ganglion cells.

Seven days after optic nerve transection, the mean density of retinal ganglion cells decreased significantly to 54% in unstimulated controls. Electrical stimulation significantly increased the density of surviving retinal ganglion cells in a dose-dependent fashion. The maximal response was to 50 μA, which increased survival of retinal ganglion density to 83% of normal. Current intensities higher than 50 μA yielded lower retinal ganglion cell densities. Sham stimulation showed no rescue effect.

The authors found that electrical stimulation enhanced survival of axotomized retinal ganglion cells. The mechanism underlying this enhancement is unknown but cell depolarization is known to activate a number of neurotrophic signaling pathways. These results may have implications for repairing or saving damaged optic nerves.
Optic nerve injury in adult mammals causes retinal ganglion cell death. Restoring function requires rescuing retinal ganglion cells and inducing regeneration of their axons. Axotomized retinal ganglion cells are rescued by bcl-2, an antiapoptotic gene. However, the effect of bcl-2 on axonal regeneration is less clear.

In the current study, retinal ganglion cell survival and axonal regeneration through a peripheral nerve graft were compared in transgenic mice that overexpress bcl-2 and wild-type mice after optic nerve transection. Enhancement of axonal regeneration has been shown in the presence of peripheral nerve transplants at the transection site.

Bcl-2 mice had a higher survival rate (nearly 10 times greater) of retinal ganglion cells than wild-type mice after optic nerve transection. However, the axonal regeneration rate in bcl-2 mice was unexpectedly much lower than that in wild-type mice. Even when corrected for the total number of retinal ganglion cells, the axonal regeneration rate in bcl-2 mice did not exceed that in wild-type mice. This indicates that the majority of surviving retinal ganglion cells in bcl-2 mice failed to regenerate their axons despite the peripheral nerve graft. Examination of the grafts revealed some retinal ganglion cell axons regrowing intraretinally and repulsed at the optic disc.

The authors concluded that bcl-2, an antiapoptotic gene, promotes retinal ganglion cell survival but not axonal regeneration after optic nerve transection. A combination of retinal ganglion cell survival and axonal regeneration is necessary to restore optic nerve integrity after physical damage. Further work on promoting axonal regeneration will be necessary if restoring optic nerve function after damage is to be achieved.

Attempts to promote CNS recovery after injury are often limited by the death of large numbers of neurons soon after the damage. Various trophic factors have been used to prevent cell death after injury but their effects are transient. Brain-derived neurotrophic factor (BDNF), for example, is a potent inhibitor of retinal ganglion cell death after optic nerve damage. However, even when BDNF is repeatedly or continuously applied, the neuroprotective result is not sustained and eventually retinal ganglion cells die.

The authors hypothesized that the neuroprotective effect of BDNF is short-lived because the retinal ganglion cell response to this trophic factor is compromised by the injury. To investigate this, they first looked for changes in gene expression of the BDNF receptor, TrkB, after axotomy in rats. In an attempt to enhance retinal ganglion cell survival, copies of the TrkB gene were transfected into retinal ganglion cells to upregulate expression of this receptor.

Retinal ganglion cell TrkB mRNA expression was significantly decreased after axotomy and this decrease occurred before the onset of retinal ganglion cell death. TrkB gene transfer to retinal ganglion cells before axotomy increased neuronal survival. Survival was further enhanced if BDNF was injected into the vitreous at the time of axotomy.

These data show that the expression of TrkB is downregulated in retinal ganglion cells after axotomy but before neuronal death. This downregulation may be the basis of the inability of BDNF to promote survival of injured neurons in a sustained fashion. When the expression of TrkB is augmented in vivo by transfecting retinal ganglion cells with its gene prior to axotomy, more ganglion cells survive. Ganglion cell survival is better still if TrkB gene transfection is combined with injection of BDNF into the vitreous. This strategy may have therapeutic potential in optic nerve and other CNS injuries.

VI. Eye Movements


Recent evidence suggests that activity of basal ganglia neurons is modulated by reward or motivation. The basal ganglia become involved with eye movements through a proposed pathway from the caudate nucleus to the substantia nigra pars reticulata (SNr) to the superior colliculus. The caudate nucleus sends both direct inhibitory and indirect excitatory projections to SNr. SNr then exerts its effects on saccades via its strong inhibitory projections to the superior colliculus. Single cell recordings from the caudate nucleus have revealed neurons with saccadic and reward-predicting activity. Neuronal activity in SNr is also saccade related, especially when saccades are guided by memory, but whether activity in SNr is modulated by reward is unknown.

This study tested the hypothesis that basal ganglia neurons participate in reward-oriented saccadic activity. Single cell recordings were obtained from SNr in primates performing a memory-guided saccadic task. Monkeys had to make a saccade to a previously cued and memorized location that varied in position about a central fixation point. In some sets of trials, correct saccades to all locations were rewarded. In other sets, saccades to all locations were required but only those to a single location were rewarded.
Spike activity of SNr neurons after the cue was determined by the position of the cue and the reward that would be given after the trial. Baseline spike activity could either increase or decrease as a function of one or both of these factors. Some neurons, for example, exhibited decreased spike activity to a cue in a particular location in space. When that cue indicated an upcoming reward, the decrement in spike activity was even greater. This reward-related modulation of activity was greater in the task where only one location was rewarded than in the task where all locations were rewarded. The post-cue activity of most neurons (whether inhibition or increase in spike activity) was larger for contralateral than ipsilateral cues.

These results indicate that neuronal activity of SNr neurons is modulated by opportunity for reward. The most common type of neuron found in SNr had spike activity that was inhibited by a contralateral cue and more so when the cue signaled a reward. Via their inhibitory projections, such neurons would disinhibit neurons in the superior colliculus, leading to a saccade toward the position of the contralateral cue. The disinhibition would be greater in trials where the cue signaled a reward, possibly leading to an earlier and faster saccade. This study provides important insight into the mechanisms underlying saccadic eye movements and may have clinical implications for patients with basal ganglia disease.

Neuroclinical Journals

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I. Cerebrovascular Disorders


Most cavernous sinus dural AVMs carry a relatively low morbidity and mortality. Conventional angiography is usually not necessary to diagnose the condition. In rare instances, however, the AVM may lead to intracranial hemorrhages or venous infarctions because of high pressure on cortical veins. The recommended treatment is then prompt angiographic confirmation and closure of the AVM.

The authors retrospectively reviewed the records and cerebral angiograms of 118 patients with cavernous sinus dural AVMs to determine which signs and symptoms predicted the presence of cortical venous drainage (CVD). They detected CVD in 22 of the 118 patients (19%). The three features associated with an increased risk of CVD were: 1) bilateral orbital congestion (the presence of more than one of the following: proptosis, chemosis, increased IOP, venous stasis retinopathy, extracocular muscle dysfunction, choroidal effusions and optic neuropathy); a 2) post-auricular bruit audible to the examiner; and 3) signs of CNS dysfunction.

Bilateral orbital congestion was present in 28 patients, 43% of whom had CVD, whereas only seven of 30 patients (9%) with unilateral orbital signs had CVD. An audible postauricular bruit was present in four patients, two of whom had CVD. The seven patients presenting with CNS dysfunction (intracerebral hemorrhages, transient ischemic episodes, or dizziness/vertigo) had CVD.

The authors recommend conventional angiography for patients with any of these three features. Those without them are at relatively low risk for the development of CVD and may be followed with conventional MRI and MRV studies. Of course, treatment might be indicated for other reasons, such as intractable pain, refractory high intraocular pressure, visual loss, or diplopia.


The authors evaluated 110 patients with symptomatic carotid artery occlusion (CAO) for signs of venous stasis retinopathy (VSR) and ocular ischemic syndrome (OIS). All patients presented with a history of either a transient ischemic episode or minor stroke involving the brain or retina ipsilateral to the CAO. VSR was diagnosed if at least one of the following findings was present: midperipheral microaneurysms, dot-and-blot or splinter hemorrhages, cotton wool spots, or dilated or irregular retinal veins. OIS was diagnosed if at least one of the following was also present: neovascularization of the optic disc, retina, or iris or neovascular glaucoma.

Cerebral blood flow was examined using cerebral arteriography, transcranial Doppler (TCD), and magnetic resonance angiography (MRA).

Of the 110 patients, 32 (29%) had signs of VSR, including midperipheral hemorrhages in all 32, venous dilatation in 16, microaneurysms in three, and cotton wool spots in two. OIS was not found in any patient at the time of enrollment. There was no difference in visual acuity or intraocular pressure between patients with or without VSR. Transient monocular blindness or retinal infarction did not occur more frequently in patients with VSR. Retinal claudication, defined as transient blindness after exposure to bright light, was reported by only three patients, two with VSR.

Reversal of blood flow in the ophthalmic artery as measured by TCD was no more common in patients with (94%) than without (84%) VSR. However, patients with VSR had a lower CO2 reactivity and lower pulsatility index.
of the cerebral arteries, indicating that the cerebral arteries in patients with VSR were compensating for impaired cerebral blood flow by maximal dilatation.

During a mean follow-up period of 29 months (range 2–50 months), three of the 32 patients with VSR developed OIS, whereas none of the other 78 patients did. Unfortunately, the patients without VSR at enrollment were not re-examined unless they developed visual symptoms, so that some patients may have developed asymptomatic VSR or OIS.

The authors recommended that patients with CAO undergo repeated ophthalmological examinations regardless of whether they have visual symptoms or not. If VSR is present, more careful follow-up is indicated to ensure that if OIS develops, it can be treated before irreversible retinal or optic nerve ischemic damage occurs.

Because of the small number of patients with VSR and the lack of randomization of treatment, the authors could not determine whether surgical intervention (contralateral internal carotid artery endarterectomy or EC/IC bypass) prevents or treats VSR or OIS.

II. Intracranial Hypertension


Corbett JJ, Digre K. Idiopathic intracranial hypertension. An answer to "the chicken or the egg?" Neurology 2002;58:5–6.

The cause of idiopathic intracranial pressure (IIH) remains unknown, but recent evidence has suggested increased cerebral venous pressure (CVP) as the underlying cause. Studies conducted on obese patients with IIH during gastric bypass surgery have shown increased intraabdominal pressure and increased CVP that may lead to increased right heart pressures and impaired cerebral venous drainage.

The authors studied 21 patients diagnosed with IIH with cerebral dural sinus venography. They noted increased venous pressure within the superior sagittal sinus and a large pressure drop across the transverse sinus (9–46 mmHg), supporting the theory that IIH is caused by increased cerebral venous pressure. The authors then studied eight additional IIH patients using dural sinus venography and CSF manometry before and after they lowered the intracranial pressure by removing 20–25 mL of cerebrospinal fluid (CSF) via C1-C2 cisternal puncture. They reported a dramatic decrease in pressure throughout the cerebral venous system after the intracranial pressure was lowered, indicating that the venous pressure elevation in IIH is secondary to increased ICP. In an accompanying editorial, Corbett and Digre state that “the chicken is the CSF pressure elevation and the egg is venous sinus pressure elevation.”


The authors report a case of sagittal and transverse sinus thrombosis in a previously healthy 26-year-old professional cyclist who was illicitly injecting erythropoietin to enhance endurance by increasing packed cell volume (PCV). He presented with headaches, mild papilledema, and increased CSF opening pressure. A cranial MRI revealed sagittal and transverse sinus occlusions. An extensive coagulopathy evaluation was negative, except for an increased red blood cell count (5.4x1012/L (normal 3.5–5.0) and increased PCV of 0.51 (normal 0.39–0.49). He was treated with hydration and phlebotomy; within several months, the venous sinuses had recanalized and the headaches and papilledema had resolved.

Clinical trials using erythropoietin to treat anemia in dialysis patients have shown an increased risk of cardiovascular and cerebral ischemic events even when the hematocrit remains within normal limit, suggesting that the drug itself is prothrombotic. The authors recommend adding this drug to the list of legal and illegal agents associated with CNS thrombotic events.

III. Intracranial Tumors


The treatment of optic nerve sheath meningiomas (ONSM) is controversial. Removal of the tumor and optic nerve en bloc has been recommended for significant proptosis and no light perception, intractable pain, or significant intracranial extension of the tumor. Attempts to strip an ONSM from the optic nerve almost always lead to severe optic nerve ischemia followed by a local recurrence years later. Stereotactic radiosurgery can be used only in sightless patients because the high dose radiation leads to radiation necrosis of the optic nerve. Several recent case reports have shown promising results using conformal fractionated radiotherapy, but follow-up has been 2 years or less.

The authors report five patients with presumed ONSM treated with three-dimensional fractionated conformal radiotherapy (the largest reported series to date). Baseline visual acuity ranged from 20/20–20/40, and all five pa-
tients had diminished color vision and visual field defects. One patient had either a unilateral ONSM that extended across the planum sphenoidale or a primary planum sphenoidale meningioma causing blindness in one eye and loss of acuity to 20/40 in the other. All five patients received 1.8 Gy/session for 25–30 daily sessions (total dose of 45–54 Gy) so that each patient’s tumor was encompassed at the 90% isodose line. The patients were followed clinically and with fat-saturated, gadolinium-enhanced MRIs every 3 months for 1 to 7 years.

Four patients improved and one remained stable 2 years after treatment. None developed radiation optic neuropathy or retinopathy. Follow-up is short and the series is small, but the preliminary data show great promise.


Dorsal midbrain gliomas are rare in adults (1% of brain tumors) and more common in children (10% to 20%). Most brainstem gliomas in adults are aggressive, show marked enhancement on MRI, and are treated with radiation and chemotherapy with a poor prognosis; those in children tend not to enhance after gadolinium administration, are followed without intervention, and when studied pathologically are found to be low-grade gliomas. However, what treatment is most appropriate for adult patients with nonenhancing dorsal midbrain gliomas?

The authors followed five patients with dorsal midbrain nonenhancing masses with increased T2 and decreased T1 signal on MRI consistent with low-grade gliomas (one patient had a low grade glioma based on a biopsy taken during ventriculoperitoneal shunt placement). Two patients were diagnosed incidentally and three patients presented with signs and symptoms of obstructive hydrocephalus requiring ventriculoperitoneal shunt placement. The patients were observed for 2 to 9 years (mean 4 years), and none deteriorated clinically or showed signs of tumor growth on MRI. These observations coincide with previous studies in children.

The major shortcoming of this study is the relatively short follow-up period. Although the study supports conservative follow-up of low grade midbrain gliomas in adults, there is a reported case of an adult with a nonenhancing low-grade dorsal midbrain glioma that was not treated and remained unchanged for 5 years but later grew, developed gadolinium enhancement, and proved to be an anaplastic astrocytoma. (Oka K, Kin Y, Go Y, et al. Neuroendoscopic approach to tectal tumors: a consecutive series. J Neurosurg 1999;91:964–70.)

The authors report a 42-year-old male presenting with headaches and vertigo who was found to have a large inhomogeneously enhancing mass centered in the preoptic cistern causing extrinsic brainstem compression. Apart from diminished hearing on the left, neurologic examination was unremarkable, including ocular motility. The mass was completely removed although adherent to the left sixth nerve and found to be a schwannoma. Immediately after surgery, the patient developed a partial sixth nerve palsy that resolved within 1 year.

The authors point out that schwannomas affect cranial nerves in this decreasing order of frequency: eighth, fifth, seventh, ninth, tenth, eleventh, twelfth, third, and sixth nerves. They summarize ten other reported cases of sixth nerve schwannomas. The tumors have arisen either within the cavernous sinus or the preoptic cistern. All have presented with clinical deficits in other lower cranial nerves or the brainstem; three presented with signs of obstructive hydrocephalus. Posterior fossa schwannomas generally have different MRI and CT characteristics than meningiomas, such as inhomogeneous enhancement, cystic degeneration, lack of a dural tail, and lack of calcifications on non-contrast CT so common in meningiomas.


The authors report the case of a 21-year-old female with an 8-year history of painless, progressive visual loss OS, and evidence of an optic neuropathy without proptosis or impaired ocular motility. Serial non-fat-saturated MRIs noted a nonenhancing high T1 signal mass involving the intracanalicular portion of the nerve with intracranial extension. The mass lost its increased T1 signal after fat saturation. The differential diagnosis included an optic nerve lipoma, choristoma, atypical meningioma, glioma, lymphoma, and a chronic inflammatory process. Surgery disclosed a fatty tumor interdigitating itself between optic nerve fascicles. It was resected with the optic nerve en bloc. Pathologically, the presence of adipose tissue and mature smooth muscle tissue indicated an optic nerve choristoma. The term choristoma refers to the proliferation of normal mature tissue in an abnormal location; most orbital choristomas involve the adnexa or choroid.

The authors point out that five other reported cases of optic nerve choristoma have presented in a similar way with slowly progressive optic neuropathy. Three cases had involvement of the chiasm radiologically but not clinically.
IV. Denaturing Disease


The authors discuss the potential uses of magnetic resonance spectroscopy (MRS) in the diagnosis and treatment of MS. Unlike MRI, which measures nonspecifically altered tissue water properties, MRS assesses biochemical functions by measuring various bioactive compounds, including N-acetylaspartate (NAA), a marker for neuronal or axonal integrity, choline, a marker of cell membrane turnover, lactate, a marker of anaerobic metabolism, glutamate, a marker of excitatory neurotransmitter function, and creatine, a reference marker.

An acute, gadolinium-enhancing MS plaque has elevated choline and lactate peaks on MRS, indicating damage to myelin. The NAA peak is diminished, indicating axonal damage. After an acute plaque “heals” on MRI, the NAA, choline, and creatine peaks often normalize. If an MS plaque becomes a T1 “black hole,” the MRS often shows a persistently depressed NAA peak, reflecting irreversible axonal loss.

MRS has also been used to study “normal appearing white matter” on conventional MRI. An increase in the choline peak can precede the development of a visible MRI plaque by several months; depression of the NAA peak is often found in normal white matter surrounding plaques as an indication of more extensive axonal damage than visualized by MRI. Conventional MRI scans rarely detect cortical MS plaques (although they are visible pathologically), whereas MRS often detects abnormal choline and lactate peaks involving the cortex. Reduced whole brain NAA levels also correlate well with T2 lesion load.

MRS still remains a research tool, but it is likely to play an important role in the evaluation of patients early in the course of their illness, when conventional MRI may underestimate the extent of disease. MRS may also assist in the management of patients who are declining neurologically but whose MRI scans show little or no change.


The authors studied 107 patients presenting with acute, monocular optic neuritis who underwent fat-saturated, gadolinium-enhanced MRI of the orbits before being offered treatment with steroids. The mean time between symptom onset and MRI was 8.7 days (range 1-19 days). Enhancing optic nerves were found in 101 (94%) of the patients. Enhancement of the intracanalicular optic nerve correlated with worse baseline color vision ($P < 0.05$), whereas enhancement of intraorbital, intracanalicular, and intracranial segments correlated with worse baseline threshold static perimetry ($P = 0.001$) and color vision ($P < 0.01$). Enhancement of > 10 mm of the optic nerve correlated with worse baseline threshold static perimetry ($P = 0.004$), whereas enhancement of > 17 mm of the optic nerve correlated with worse baseline visual acuity ($P = 0.02$), static perimetry ($P < 0.01$), and color vision ($P = 0.01$).

Visual improvement occurred in all groups, and by 1 month there was no difference between the steroid-treated and untreated patients (treatment was not randomized). The improvement also applied to those patients with intracanalicular enhancement or enhancement of > 17 mm of the nerve. This finding contradicts that of previous studies, which indicated that patients with intracanalicular or extensive optic nerve involvement tend to recover more slowly with more severe residual deficits.


The authors presented the largest pathologic study to date of neuromyelitis optica (NMO), or Devic disease, an often destructive form of demyelinating disease involving the optic nerves and spinal cord. They compared autopsy specimens from nine patients with NMO with 73 with multiple sclerosis (MS). The mean age of the NMO patients was 50 years (range 16 to 80 years), the mean disease duration was 2.4 years, and the mean interval between the development of optic neuropathy and transverse myelitis was 19 months (range 4 to 41 months). All patients died of respiratory failure. Distinctive clinical features of NMO included normal brain MRI scans in the vast majority, longitudinally extensive signal abnormalities in the spinal cord during acute attacks (extending over 3 to 4 spinal segments), occasionally prominent CSF pleocytosis with a polymorphonuclear predominance, and poorer clinical recovery from attacks compared with MS patients.

A total of 82 lesions were examined from nine patients with NMO and were classified as “early active” if demyelinating lesions contained macrophages reactive to myelin oligodendrocyte glycoprotein (MOG), “late active” if the lesions contained more myelin degradation and macrophages reactive to myelin basic protein (MBP) and proteolipid protein (PLP) but not MOG, “remyelinating” if lesions contained thin and irregularly arranged myelin sheaths, and “inactive” if lesions showed no evidence of remyelination. Twenty-one lesions were classified as early active, 18 late active, eight remyelinating and 35 inactive. Acute NMO lesions demonstrated extensive macrophage...
and macroglial infiltration with necrosis of the optic nerves and spinal cord (gray and white matter). The inflammatory infiltrates seen in acute NMO lesions were characterized by extensive perivascular infiltration by macrophages, microglia, B lymphocytes, eosinophils, and granulocytes. Acute MS lesions also showed macrophage and microglial infiltration but the inflammation was localized in oligodendrocytes along the active plaque margin rather than in a perivascular pattern as seen in acute NMO lesions. The authors reviewed autopsy specimens from 73 patients with MS and found that eosinophilic infiltration was rarely seen (4%) but was common in NMO lesions (56%). Chronic NMO lesions demonstrated extensive gliosis, cavitation, and atrophy of the optic nerves and spinal cord.

The authors suggest that because acute NMO lesions show extensive eosinophilic and lymphocytic infiltration in a perivascular pattern, the disease may be caused by a primary vascular autoimmune disorder. They also report that rats sensitized with soluble MOG develop a chronic demyelinating disease most prominent in the optic nerves and spinal cord. The active lesions contain lymphocytes and eosinophils and show signs of humoral immunity similar to NMO. The authors theorize that because the optic nerves and spinal cord have the weakest blood-brain barrier (BBB), perhaps antigenic proteins preferentially cross the BBB in these areas in susceptible patients. Alternatively, CNS damage releases antigenic proteins, which reach the perivascular space and are recognized by immune cells within the circulation.

V. Progressive supranuclear palsy


The authors studied the autopsy specimens of patients with typical (11) and atypical (15) progressive supranuclear palsy (PSP) to determine if anatomic or genetic differences exist. They defined typical PSP by the presence of a supranuclear vertical gaze palsy, progressive gait disorder with a tendency to fall backwards, L-dopa unresponsive Parkinsonism, axial rigidity, and pseudobulbar palsy. They defined atypical PSP by the presence of prominent cortical dysfunction early in the course, idiopathic Parkinson disease-like presentation with asymmetric onset and a good response to L-dopa and relatively preserved balance and gait. Previous pathologic studies of PSP patients have revealed deposition of abnormally hyperphosphorylated tau-containing neurofibrillary tangles (NFT) in the globus pallidus, subthalamic nucleus, substantia nigra, and reticular formation of the midbrain andpons. NFTs in the midbrain presumably cause the supranuclear vertical gaze palsy.

Previous genetic studies of PSP patients have found a “PSP susceptibility gene” called the tau H1 haplotype and the authors determined that all eleven of the typical PSP patients in their study were homozygous for the H1 haplotype, whereas only eleven of the fifteen (73%) atypical cases were homozygous. Eight of the eleven patients (70%) with typical PSP had detectable levels of PSP tau protein in CNS tissue, whereas only five of the fifteen (33%) atypical PSP patients had PSP tau protein. The majority of the atypical patients had a tau deposition pattern indicative of Alzheimer disease: NFTs and plaques more extensively deposited within the cortex than in the basis pons.

The authors suggest that several discrete clinicopathologic entities may exist within the spectrum of clinical PSP. They believe that PSP-specific tau deposition and the PSP susceptibility genotype H1H1 indicate typical PSP. Lack of the tau susceptibility genotype H1H1 indicates atypical PSP. This information is useful for diagnostic and research purposes but has little clinical utility.

VI. Pregeniculate blindness and transcranial magnetic stimulation


The authors used transcranial magnetic stimulation (TMS) of the occipital lobes to study visual perception of patients with poor (20/400 to light perception) or absent vision of at least 10 years duration. TMS of the occipital lobes normally induces brief phosphenes. The authors hypothesized that a visually impaired patient’s ability to experience phosphenes by TMS could be used as an indicator of the functional integrity of the visual cortex and might aid in the preoperative evaluation of patients considered for implantation of cortical stimulators.

TMS was performed using a figure-of-eight shaped coil (radius of one half coil = 6 cm) placed over various points on a surface grid overlying the occipital lobes. Seven consecutive impulses at 15 Hz were used with an intensity of 1.3 times the individual motor threshold. In normal control subjects, transcranial stimulation elicited white phosphenes, usually in the contralateral hemifield. All ten patients with acuities between 20/400 and counting fingers perceived the phosphenes, although at fewer locations than did the control group. Nine of the fifteen patients with hand motion to light perception vision perceived phosphenes but often required a higher stimulus intensity and responded at fewer stimulation sites. Only two of the ten patients with no light perception reported seeing phosphenes and then only at very high stimulus intensities.

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This study shows that patients who are completely blind for more than 10 years are less likely to respond to TMS and theoretically less likely to respond to cortical stimulation by a visual prosthesis.

VII. Leber Hereditary Optic Neuropathy


The authors found a novel mitochondrial DNA mutation (4171) in two Korean families with Leber hereditary optic neuropathy (LHON) in the gene ND1 involved in the normal function of complex I of the electron transport chain. The three most common LHON mutations, 11778, 3460 and 14484, which account for 85% to 90% of cases worldwide, also encode proteins in complex I.

One proband was a 17-year-old male with a history of painless, progressive vision loss to counting fingers, first affecting the OS and two weeks later, the OD. The right optic disc was slightly blurred and the left showed subtle temporal pallor. Eleven months later, visual acuity spontaneously improved to 20/200 OD and 20/30 OS and the dense bilateral eccentric scotomas noted on initial Goldmann kinetic visual fields decreased in size. The patient's maternal grandmother (age 67) had developed bilateral vision loss at age 27 and recovered 3 years later. Her most recent ophthalmological examination revealed visual acuities of 20/40 OD and 20/25 OS with bilateral temporal disc pallor and pathologic cupping. The patient's maternal uncle (age 46) had suffered acute bilateral vision loss at age 19 which improved 6 months later and on a recent examination had visual acuities of 20/20 OU with temporal disc pallor and pathologic cupping.

The other proband was an 8-year-old boy who presented with painless progressive vision loss OD followed by similar loss OS 4 months later and visual acuities of 20/400 OU. Both optic discs were hyperemic with telangiectatic disc vessels and subtle temporal disc pallor. Two years later, visual acuity improved to 20/20 OD and 20/40 OS with normal color vision using Ishihara plates and essentially normal computerized static visual fields.

Sequence analysis of the entire mtDNA of the first proband found one novel mutation at position 4171. The mutation was homoplasmic in all affected members of both families and the second proband's mother was heteroplasmic (38%). The mutation substitutes a methionine for the normal leucine at codon 289 of the ND1 gene. Although both leucine and methionine are large, hydrophobic, nonpolar amino acids, the substitution alters the aliphaticity of an extramembrane loop. The 4171 mutation was not found in 514 controls or 63 documented LHON lineages.

All four patients with the 4171 mutation improved to > 20/40 in at least one eye. Fewer than 10% of patients with either the 11778, 3460 or 14484 mutations sustain this degree of visual improvement. Perhaps the subtle molecular change in the ND1 encoded protein caused by the methionine for leucine substitution explains why these patients have a much better prognosis than the vast majority of LHON patients.

VIII. Lagophthalmos


The authors hypothesized that the lagophthalmos sometimes found in patients with lower motor neuron facial nerve palsy is the result of stiffness of the levator palpebrae rather than weakness of the orbicularis oculi. Supportive evidence for their theory includes the observation that lagophthalmos persists during sleep and that the palpebral fissure widens during downward eye movements, indicating impaired relaxation of the levator palpebrae muscle. The authors consider this rigidity of the levator palpebrae muscle analogous to that of a skeletal muscle that has been splinted; the muscle becomes rigid due to the formation of tight crossbridges between actin and myosin fibers.

The authors studied thirteen patients with lower motor neuron facial nerve palsies (nine due to Bell palsy) between 1 day and 6 months (mean 18 days) after onset. They measured the degree of lagophthalmos before and again after passive closure of the eye for 15 seconds, an action that stretches the levator palpebrae muscle and breaks the actin–myosin crossbridges. The mean baseline degree of lagophthalmos was 7.0 mm (range 5–9 mm, standard deviation 1.2 mm) and the mean after passive eyelid closure decreased to 2.0 mm (range 0–3.0 mm, standard deviation 0.9 mm).

The authors suggest that patients with facial nerve palsies should routinely stretch their levator palpebrae on the side of a facial nerve palsy several times per day to diminish the degree of lagophthalmos and lessen the chances of developing exposure keratopathy.
Neuro-Ophthalmology, 3rd Edition


Scope: This is a multiauthored text, ably edited by Dr. Joel S. Glaser. The book covers the diagnosis and management of clinical neuro-ophthalmologic disorders encountered by ophthalmologists, neurologists, neurosurgeons, and neuro-ophthalmologists.

Contents: The book contains eighteen chapters. The first four chapters are designed to develop and refine basic neuro-ophthalmologic skills in history taking and examination. These chapters provide useful background material for trainees, primary care practitioners, and others unfamiliar with the basic approach to the neuro-ophthalmologic patient. The first two chapters, "The Neuro-ophthalmologic Case History: Elucidating the Symptoms," and "Neuro-ophthalmologic Examination: The Visual Sensory System," set the tone for the traditional systematic approach that is continued throughout the volume. The remaining chapters cover the spectrum of neuro-ophthalmologic problems in a traditional approach to signs and symptoms. Visual sensory problems are covered in separate chapters or subchapters for the retina, optic nerve, chiasm, retrochiasmal pathway, and disorders of higher visual function. Each section covers the practical aspects and nuances of eliciting the relevant history, developing a differential diagnosis, obtaining relevant laboratory and radiologic tests, and implementing a rational treatment. The sections on ocular motor disorders are similarly organized in topical neuroanatomic fashion. There is also a useful section on eye movement recording techniques by Drs. Dell'Oosso and Daroff. Additional chapters cover various problems that cut across neuroanatomic boundaries, including individual chapters on pediatric neuro-ophthalmologic, aneurysms, and AVMs, and an exceptionally well-written and practical chapter on the dizzy patient, by Dr. Ronald Tusa.

Strengths: The major strength of this volume is its uniformly systematic approach to diagnosis and management. Although it is a multiauthored text, it conveys a uniformly methodical approach that can be adopted by practitioners at any level. The information needed to develop this approach is conveyed in the first four chapters. The information needed to put the method to use is contained in the last fourteen chapters.

Weaknesses: A chapter on neuro-imaging, as part of the introduction to neuro-ophthalmologic skills at the beginning of the volume, would have been a useful addition. There have been a number of important developments in neuro-ophthalmology that are not covered, including immune therapies for demyelinating disease and newer neuro-imaging techniques. However, this is a minor criticism as the accelerated pace of progress in the neurosciences means that any text will miss some new and important developments when it reaches print.

Recommended audience: The book will be useful to practitioners at all levels who encounter neuro-ophthalmologic patients. Its readability makes it particularly attractive as a primary reference for ophthalmologists, neurologists, and neurosurgeons, but it is readable by primary care practitioners as well. Experienced clinical neuro-ophthalmologists will also gain fresh insights from the volume, since the authors are all seasoned clinicians, and their approach will generally add something new, even for the most experienced.

Critical appraisal: The editor is a highly respected neuroophthalmologist and medical educator. He has created a multiauthored text that conveys a unified and systematic approach to the diagnosis and management of clinical neuro-ophthalmologic disorders. The book provides the background for practitioners at all levels who require skills in the diagnosis and management of such patients.

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Clinical Eye Atlas


Scope: This is a 1464-page, multiauthored atlas and textbook intended for all eye-care specialists.

Contents: The book is divided into fourteen sections, covering all areas of ophthalmology. The organization of the book is very reader-friendly, including the index. Section editors are renowned in their areas and have assembled several contributing authors for their respective sections. There is very little repetition across sections, as one might fear in a book with over 50 contributors. Editors have done an exceptional job of collecting clinical photographs to augment their text. In addition, many histologic photographs are included to provide meaningful clinicopathologic correlation.

Almost every conceivable ocular condition is discussed, and in keeping with the title of the book, a representative color photograph is provided for each discussion.
The quality of the color reproductions is generally good. All conditions are summarized under the following headings: clinical features, basics, diagnosis, and management. Most atlases do not include such detail, which makes this atlas unique.

**Strengths:** This atlas is one of the best ophthalmic atlases that I have seen. It is well written, well organized, and wonderfully illustrated. In addition, it is comprehensive and user-friendly.

**Weaknesses:** There were no significant critical weaknesses to be noted here, aside from a handful of photographs (less than 10) that were too dark to discern details.

**Recommended audience:** The editors have succeeded in reaching their intended audience—all of us. Every eye-care professional will benefit by having a copy of this atlas, especially the junior and “on-call” ophthalmology resident. A professional will benefit by having a copy of this atlas, especially the junior and “on-call” ophthalmology resident.

**Critical appraisal:** Daniel Gold and Richard Alan Lewis are well-respected clinicians. They have done an exceptional job and are to be commended for their work here. One cannot help but be impressed by the monumental task of collecting so many photographs spanning such breadth; given that ophthalmology is such a visually oriented specialty, a comprehensive atlas of this quality is a must for all clinicians.

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*Emoryology of the Eye and its Adnexa,* 2nd Edition


**Scope:** This is a compact single-authored monograph describing the embryonal and fetal development of the human eye, starting with fertilization and culminating with birth. It is organized along three parallel paths: embryogenesis, organogenesis, and differentiation. As such, it is a time line and atlas of the developing eye from fertilization through delivery.

**Contents:** The book is divided into four sections. The first, embryogenesis, describes changes occurring over the first 4 weeks of fetal development. The second, organogenesis, delineates the changes expected between weeks 4 and 8; it includes the development of primary organ rudiments. The third section describes the differentiation of each of the primitive tissues into the fully active organ of the eye, and corresponds to that period which begins at the third month and ends at the ninth month of gestation. The fourth section is about changes at birth and thereafter. The text has a section of references that are both timely and classic. The index is complete and usefully organized.

**Strengths:** This monograph is an updated, revised second edition. It sequentially relates the development from cleavage, blastulation, through gastrulation and formation of the germ layers into the establishment of the eye; it describes what occurs, and on what calendar. The writing is clear and the reproductions are excellent. Figures are numerous and complimentary to the text. Thankfully, ultrastructural microscopy is kept to a minimum.

**Weaknesses:** As with any other text about embryology of the eye, this book relates changes over time, cell type by cell type. What such an approach fails to convey is the dynamics of such an extraordinary experiment of nature. One would rather read about how the disc gets to be where and what it is, at birth. Pioneer fibers and apoptosis could be incorporated as modern concepts that would do justice to a dynamic process of biology, rather than the static, common, sterile litany of ectoderm, mesoderm, and endoderm. The difficulty with the traditional model of embryology is that it allows one to follow the individual lines of a musical score, yet not quite grasp the success of the orchestration.

**Recommended audience:** This is a nice little book about embryology and embryogenesis. It does not break new ground, but it is concise enough to read, to digest, and to serve as a reference. The book will be of interest to those who wonder how the eye got to be.

**Critical appraisal:** I think most readers are looking for a new type of embryologic text, perhaps one that focuses upon tissues rather than cells, and presents material in a new and clinical matrix. A story of how the eye evolved biologically and independently, in several circumstances, would add a valued dimension to this difficult topic. Such an evolutionary approach would add an extraordinarily meaningful addition to the embryologic literature and our understanding thereof. Nonetheless, this is a fine conventional, readable, overview of the embryology of the eye and its adnexa.

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*CT of the Head and Spine*  

**Scope:** This is a comprehensive textbook that offers an overview of computed tomography (CT) of the head and
Clinical Neurology of the Older Adult


Scope: This is a multiauthored textbook of geriatric neurology. The authors are renowned researchers and clinicians who have thoroughly reviewed every aspect of neurology relevant to the older adult. Contributions come not only from neurology and neuroscience, but from internal medicine, radiology, psychiatry, and psychology. This text is extremely valuable for students and practitioners of all specialties with an interest in the older adult.

Contents: The book is divided into four sections, including 35 chapters, each offering an overview of one particular area. Section I (five chapters) provides details about the normal aging brain and its function, including information on diagnostic tests, pharmacology, and menopause. Section II (six chapters) reviews common neurologic symptoms and signs of the elderly, such as confusion, syncope, dizziness, sleep disorders, tremors, back and neck pain, incontinence, and sexual disorders. There is one chapter entitled The Neuro-Ophthalmology of the Elderly. In Section III (13 chapters), neurologic disorders are summarized as they affect the elderly, with descriptions of their resultant cognitive disorders and neuropsychologic consequences. The topics are stroke, trauma, movement disorders, peripheral neuropathies, seizures, infections, cancer, and neurologic manifestations of systemic diseases. The last section (five chapters) covers unique neurologically oriented issues of the elderly, including late life mood disorders, somatization, rehabilitation, long-term care options, and societal issues such as elder abuse and physician-assisted suicide. The appendix concludes with helpful information on organizations addressing the clinical care needs of an older population.

Strengths: The editors have brought together a wide group of contributors who have thoroughly reviewed every aspect of neurology relevant to the elderly. There are a few illustrations, all in black and white. The writing style is clear, and the chapters well organized, with abundant tables and algorithms.

Weaknesses: Some of the information included is too basic for neurologists; much of the book seems more directed to a primary care audience.

Recommended audience: This book is extremely valuable for students and practitioners involved with the elderly.

Critical appraisal: The monograph was assembled by experts in gerontology to provide accurate and timely information on the clinical care needs of the elderly. It offers much practical information, and will prove very useful to physicians treating a geriatric population, the subtleties of spine. The authors present their material and compare and contrast it to other imaging modalities, most notably magnetic resonance imaging (MRI). This approach is extremely valuable for students, residents, and practitioners with an interest in imaging of the nervous system and a desire to understand the science and application thereof.

Contents: The book is divided into two parts: CT of the head and CT of the spine. Each begins with a good review of normal anatomy as imaged by CT, as well as the clinical and technical aspects of CT technology. The material on head CT includes craniofacial trauma, cerebrovascular diseases, inflammatory diseases, intracranial tumors, degenerative and demyelinating diseases, and congenital brain conditions. There is an additional chapter on facial and skull base anatomy. The spine CT section includes functional and structural abnormalities such as syringomyelia, dysraphic disorders, spinal trauma, degenerative diseases of the spine, intraspinal masses, and inflammatory diseases.

Strengths: In this simple monograph, the authors have thoroughly reviewed the use of head and spinal CT in numerous diseases. Although the emphasis is on CT, the book contains detailed information on the current status of MRI. Indeed, at a time when clinicians and radiologists need to make a selection from the various imaging procedures available and choose the one that will be of greatest benefit to the patient, it is helpful to have such a comprehensive reference work that highlights the complementary roles of CT and MRI. There are numerous illustrations, mostly in black and white. The writing is clear and the chapters well organized, with abundant tables. The two chapters on anatomy and fundamental aspects of CT are superb.

Weaknesses: Given how good CT is for imaging of the orbit, one would have liked a chapter entirely devoted to orbital diseases. The chapter on cerebrovascular disease is too cursory. Moreover, there is only one small paragraph on CT angiography.

Recommended audience: This book is extremely valuable for students, residents, and practitioners learning the art of neuroimaging, and trying to apply it, in their clinical practice.

Critical appraisal: This very practical text provides a thorough understanding of CT of the head and spine for both reference and teaching. It will be read, re-read, and used in patient care.

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geriatric neurology for the neuro-ophthalmic community will have to be garnered elsewhere.

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Case Studies in the Neuropsychology of Vision


Scope: In the vein of Oliver Sachs' The Man Who Mistook his Wife for a Hat, this book offers a series of cases relating to various aspects of higher cortical processing of vision. It includes discussion of the neuroanatomy involved, the neuropsychologic tests used to document and measure the cognitive loss, and relates relevant experimental data and similar reported cases.

Contents: The text is divided into several sections, each authored separately. Section titles include “Motion Blindness,” “Cerebral Achromatopsia,” “Integrative Agnosia,” “Aperceptive Agnosia,” “Vision and Visual Mental Imagery,” “Optic Aphasia,” “Covert Recognition,” and “Anosognosia in Prosopagnosic Patients.” Each section typically includes an introduction of the topic, representative case presentations, analysis and description of appropriate neuropsychologic assessment, a review of the literature, and a unifying discussion.

Strengths: Each section (and case) presents an interesting example that introduces a discussion of neuropsychologic aspects of visual processing. Each case is presented in exquisite detail, including the neuropsychological testing. Findings are then correlated with experimental findings in animal models. All sections are written by experts in their field, primarily from departments of psychology throughout the world. Topics are well organized, well written, and well referenced.

Weaknesses: All the cases are interesting. At first glance the book might be thought easy reading; this turns out not to be so, as this is not an introductory text. Some basis of understanding of the more detailed aspects of visual neuropsychologic testing is presumed. This assumption is problematic for the ophthalmology-trained neuro-ophthalmologist. The last section, “Relations Among the Agnosias,” might have better been presented earlier, and a review of the basics of neuropsychologic testing would too have been useful.

Recommended audience: This book is directed towards those neurologists, psychologists, and neuro-ophthalmologists who wish to gain additional knowledge about the neuropsychology of vision, and do so in a case based method.

Critical appraisal: These cases present excellent examples of various aspects of the higher cortical functioning of vision. They stimulate the reader and present critical experimental information and discussion of visual processing. I would highly recommend this series of experiments of nature to all those who practice any aspect of neuroscience, from clinician to basic scientist.

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To the Editor:

Metamorphosia is a visual illusion that distorts the size, shape, or inclination of objects. It can be a rare manifestation of acute central nervous system (CNS) disease involving the visual or vestibular pathways (1-5). “Floor-on-ceiling” phenomenon is one of its rare paroxysmal forms, classified as reversal of visual metamorphosia (RVM). It was first described by Winslow (1) in 1868 in a patient with hysteria. It has also been reported in patients with migraine or vertebrobasilar insufficiency (1,3,4). Its pathophysiology is uncertain, but the favorable response to anticonvulsants in some cases suggests a possible hyperactivity of cortical or subcortical neurons (2). In the few available reports in the medical literature, electromyography (EG) findings have been described only during the interictal state (1-4). We report the findings of continuous video EEG monitoring performed while a patient experienced several episodes of “floor-on-ceiling” phenomenon associated with the sensation of body levitation.

A 76-year-old man with a history of hypertension and old pontine stroke was admitted to our hospital after being found conscious on the floor by his wife. While in the hospital, he developed multiple episodes of sensing 180° rotation of his visual environment in the coronal plane. Each episode lasted up to 60 minutes and was associated with a sensation of body levitation. He felt as if he was “floating above the bed,” while seeing the television set down on the floor.

His episodes were initially associated with an intense fear of falling from the bed. They were not associated with confusion, vertigo, speech changes, or other neurologic complaints. His medications included prazosin, aspirin, metoprolol, and Atorvastatin. His neurologic examination was consistent with his previous pontine stroke and revealed mild dysarthria, left facial paresis, and left hemiparesis with increased tone, hyperreflexia and Babinski sign but no sensory changes. During one of the episodes we asked him to write his name and a sentence on a piece of paper. He was still able to do it correctly although the text was rotated clockwise by about 30 degrees.

Brain magnetic resonance imaging revealed an old right pontine stroke but no evidence of acute ischemia. Magnetic resonance angiography was normal. Initially, he was experiencing 1 to 3 episodes/day. He was started on intravenous heparin, which was later stopped as the episodes persisted. During continuous 24-hour video EEG monitoring, three episodes were recorded. No abnormalities in the surface EEG were observed during the attacks. Subsequently, gabapentin was started and the episodes stopped. One month later, we slowly tapered the gabapentin. No further episodes occurred 9 months after this medication was discontinued.

To our knowledge, this is the first report of video EEG findings during episodes of RVM. The response to gabapentin could support the hypothesis of abnormal activity of subcortical nuclei, which could be missed by surface EEG tracings and thus explain the normal EEG recording in our patient. In addition, surface EEG has a relatively poor sensitivity in the confirmation of simple partial seizures, although the temporal clinical pattern does not favor this etiology. It is possible that these episodes represented transient abnormal activity of the vestibular projections, which could have generated an altered body scheme representation in the parieto-occipital cortex (1). This case suggests that episodes of RVM are not associated with ictal surface EEG abnormalities. Further studies are necessary to confirm this observation.

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REFERENCES
Bilateral Distribution of the End Branches of the Pontine Paramedian Branches of the Basilar Artery

To the Editor:

Recently, within the same week, two elderly patients were admitted to the Massachusetts General Hospital with the acute onset of a bilateral internuclear ophthalmoplegia (INO) and signs of a unilateral pontine stroke. In light of the unexplained bilaterality of the INO, I was reminded that in the past, when studying the vascular disease underlying lacunar strokes in the pons, I observed that a penetrating paramedian branch of the basilar artery, when approaching the floor of the fourth ventricle, could bifurcate, sending terminal branches to both the ipsilateral paramedian pons and the contralateral mirror territory. Since the medial longitudinal fasciculus lies in the posterior pontine paramedian region on each side, the division of the terminal arterioles described could explain the occurrence of bilateral INOs in an otherwise unilateral pontine stroke.

The observations were made in horizontal serial section preparations of the pons in cases of lacunar infarction. The sections were 8 μm thick and the series was continuous. The phosphotungstic acid-hematoxylin staining method was used. Arteries could be traced in continuity down to their finest twigs. This terminal branching was noted in several instances but only in passing, and a methodical study was not made since it was not relevant to the investigation on the nature of the vascular occlusion. My recollection, however, is quite definite. Support for the validity of the present suggestion is provided by a case of proved basilar branch occlusion in which the patient, clinically, had exhibited a one-and-a-half syndrome. (1)

The matter is important in the stroke field where bilateral signs indicate basilar trunk occlusion and potential disaster, whereas a unilateral lesion is consistent with a less threatening basilar branch occlusion. Also, at times, the precise neuro-anatomic organization at the level of the sixth nerve nuclei seems unclear clinically, possibly because of vascular factors.

A restudy of the vasculature using serial sections should be feasible in experienced hands. Pathological study in a clinically studied case of INO would, of course, be preferable. Injection of the paramedian arteries of the freshly removed brain at autopsy could be tried, using India ink or other material. The postmortem radiographic studies of Hassler (2) used injection into the basilar artery, thus producing bilateral filling.

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REFERENCES

Asymmetric Myopia Developing After Optic Neuritis

To the Editor:

The relationship between anisometric refractive error and amblyopia is commonly understood to be that the former may often cause the latter. Some researchers though, have recently postulated the opposite—that amblyopia can actually cause hyperopia to develop in some children, and that it can interfere with a young eye’s expected tendency to become more myopic over time. The patient described here provides anecdotal evidence to support the causative role of amblyopia in the development of anisometropia.

A 7-year, 9-month-old girl presented with unilateral optic nerve edema resulting from post-viral optic neuritis. Her visual acuity was correctable to 20/400 in the involved OS, and was 20/15 uncorrected in the OD. Six months earlier, an examination had found 20/15 uncorrected acuity in OU and no other ocular abnormalities.

After normal laboratory and radiologic evaluations, a neuro-ophthalmologist prescribed a short course of prednisone. Within a month, uncorrected visual acuity had returned to 20/20 in the affected OS, although color and contrast perception remained subjectively impaired.

The unaffected OD gradually became myopic. Within a year, it measured −0.75 sphere. Two years later, it was −1.25 sphere, and after seven years, was −2.25 sphere. Meanwhile, the affected OS became hyperopic, with a cycloplegic refraction of +0.50 sphere. Axial length also became asymmetric. After 7 years, the myopic OD’s axial length was 23.30 mm, while the OS, having recovered from optic neuritis, measured only 22.35 mm. There has been no recurrence of optic nerve inflammation and no sign of an associated systemic disease.

The various intertwined factors that control eye growth and emmetropization are poorly understood. Among the many presumptive causes of myopia are genetic factors, excessive near work (1), high level of education, perinatal ambient lighting conditions, and ocular occlusion or visual deprivation or defocus (2,3). Genetic characteristics and early visual experience seem to determine an eye’s expected tendency to become more myopic (4).

The case described here raises questions that may help to illuminate the relationship between these influences. This child’s impaired eye remained emmetropic, while the fellow eye, normal and unaffected by optic neuritis, developed progressive axial myopia.
Emmetropization appears to be an active process that is not yet fully understood (5). As a child’s eye grows, the refractive error typically becomes less hyperopic and approaches emmetropia. Several studies have shown, however, that normal emmetropization and eye growth can be prevented by various interventions. Myopia can be produced by wearing spectacle lenses that impose hyperopia and by visual deprivation. In chicks, hyperopia can be caused by sectioning the optic nerve or by raising visually immature birds in constantly lighted conditions.

In this case, the child’s normal eye grew to be about 3.8% longer than the eye affected by optic neuritis. Kiorpes and Wallman (6) showed that when experimental unilateral amblyopia was induced in monkeys, hyperopia tended to develop in these eyes within only a few months of the onset of amblyopia. Meanwhile, the untreated normal eyes became myopic, their axial length increasing by an average of 3% (6). In their study, amblyopia seemed to interfere with the eye’s normal growth toward myopia. Rather than being a result of the eye’s hyperopic error, experimental amblyopia actually seemed to cause the hyperopia to develop.

Our case would seem to be a natural experiment that supports the unorthodox view that amblyopia may in some circumstances cause anisometropia, rather than the reverse. Controlled human studies will likely be impossible to perform, but other similar cases might confirm or refute this impression.

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REFERENCES

Migraine-like Visual Hallucinations in Occipital Lesions of Cysticercosis

To the Editor:
I read with great interest the article by Sharma et al (1) about migraine-like visual hallucinations in occipital lobe lesions of cysticercosis. All four patients presented with episodic visual hallucinations. Neuroimaging revealed single enhancing computed tomographic (CT) or magnetic resonance (MR) imaging lesions. Such single enhancing CT/MR lesions are the most common imaging abnormality in Indian patients with new-onset seizures (no relevant references are provided by the authors). The seizures are often partial (motor > sensory) with or without secondary generalization.

If the lesion is located in the occipital lobe, episodic visual hallucinations may be the only ictal manifestation. More often, visual manifestations precede motor convulsions (2–4). Histopathologic studies of these lesions in India and even in some developed countries have revealed that neurocysticercosis is the most likely cause, provided they fulfill a rigid set of clinical and radiologic criteria. Single cysticercus granulomas measure less than 20 mm in diameter, may be associated with cerebral edema not severe enough to displace midline, and occur in patients with seizures, a normal neurologic examination and no evidence of active systemic disease.

The next most common cause of these lesions is tuberculosis, clinical and imaging features are similar to cysticercosis (5,6). Because of similarities in clinical and imaging characteristics, it is difficult to differentiate between tuberculoma and single cysticercus granuloma (7,8). Serologic tests for cysticercosis, enzyme-linked immunosorbent assay (ELISA), and the enzyme-linked immunotransfer-blot (EITB or immunoblot) display poor sensitivity in detecting antibodies in cases of single lesions and sensitivity is very low (range 14–45%) (2). The most interesting feature of single cysticercus granuloma is their spontaneous disappearance within a few weeks or months (2–4). Some lesions heal with calcification. These patients need only antiepileptic therapy. Antiepileptic drugs may safely be withdrawn after CT lesions have disappeared (9). Contrary to what has been done in this series (1) treatment with albendazole has not been found effective. Padma et al. (10) in a placebo-controlled study observed that treatment with albendazole did not hasten the resolution of CT lesion.

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REFERENCES

Upcoming Meetings

June 15–18, 2003
European Neuro-Ophthalmological Society (EUNOS)
Göteborg, Sweden
http://www.oft.gu.se/eunos2003
Contact: Bertil.Lindblom@neuro.gu.se

June 17–21, 2003
Canadian Congress of Neurological Sciences Annual Meeting
Quebec, Canada
http://www.ccns.org
Contact: congress@venuewest.com

June 20–22, 2003
45th Annual Scientific Meeting of the American Headache Society
Chicago, IL
http://www.ahsnet.org/
Contact: alshq@tailey.com

July 10–15, 2003
Sixth IBRO World Congress of Neuroscience
Prague, Czech Republic
Contact: krajidlova@guarant.cz

July 23–25, 2003
The 26th Annual Japan Neuroscience Meeting
Nagoya Congress Center
Nagoya, Japan
http://www.med.nagoya-u.ac.jp/molneuro/dir/jnns26/indexe.html
http://www.nerv.or.jp/nic_e/index.html
Contact: +81-52-683-7711

August 30–September 2, 2003
7th European Federation of Neurological Societies Congress
Helsinki, Finland
http://www.efnes.com/efns2003/
Contact: headoffice@efnes.org

September 14–18, 2003
XVth International Congress of Neuropathology
Turin, Italy
http://www.newtours.it/icnp2003/
Contact: ICNP2003@newtours.it

October 8–11, 2003
Joint European Research Meeting in Ophthalmology and Vision
Palacio de Congresos del Colegio Oficial de Médicos
Alicante, Spain
http://www.ever.be
Contact: secretariat@ever.be

October 18–23, 2003
Congress of Neurological Surgeons
Denver, CO
http://www.neurosurgery.org/cns/meetings/index.asp
Contact: 877-517-1CNS

October 19–22, 2003
American Neurological Association
San Francisco, CA
http://www.anes.org/
Contact: susanmhamilton@msn.com

November 8–12, 2003
Society for Neuroscience Annual Meeting
New Orleans, LA
http://www.sfn.org/
Contact: bj@sfn.org

November 16–19, 2003
American Academy of Ophthalmology Annual Meeting
Anaheim, CA
http://www.aao.org/annual_meeting
Contact: meetings@aaao.org

December 12–14, 2003
Japanese Neuro-Ophthalmology Society
Kyoto, Japan
http://www.mielparque.or.jp/kyt/kyt01.html
Contact: +81-75-352-7444

February 5–7, 2004
International Stroke Conference
San Diego, CA
LaRita Edwards: 214-706-1100
Contact: strokeconferences@heart.org

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March 27–April 1, 2004  
Renaissance Orlando Resort at SeaWorld  
Orlando, FL  
http://www.nanosweb.org/meetings/  
Contact: 860-586-7507  

April 24–May 1, 2004  
56th Annual Meeting of the American Academy of Neurology (AAN)  
San Francisco, CA  
http://www.aan.com/professionals/index.cfm  
Contact: 651-695-1940; web@aan.com  

April 25–30, 2004  
The Association for Research in Vision and Ophthalmology (ARVO)  
Fort Lauderdale, FL  
http://www.arvo.org/  
Contact: 240-221-2900  

May 1–6, 2004  
American Association of Neurological Surgeons 2004 Annual Meeting  
Orlando, FL  
http://www.neurosurgery.org/aans/meetings  
Contact: 847-378-0500; info@aans.org  

May 12–14, 2004  
13th European Stroke Conference  
Mannheim-Heidelberg, Germany  
Contact: Hennerick@eurostroke.org  

May 22–25, 2004  
The Society of Neurological Surgeons 2004 Annual Meeting  
Louisiana State University  
New Orleans, LA  
http://www.societyns.org/meeting/index.html  

June 5–11, 2004  
42nd Annual Meeting of the American Society of Neuroradiology (ASNR)  
Washington State Convention & Trade Center  
Seattle, WA  
http://www.asnr.org/asnr/UpcomingMeetings.htm  
Contact: 630-574-0220  

June 23–26, 2004  
5th World Stroke Congress  
Vancouver, BC, Canada  
http://www.kenes.com/stroke2004/  
Contact: stroke2004@kenes.com  

June 29–July 2, 2004  
16th International Perimetric Society Meeting  
Barcelona, Spain  
http://webeye.ophth.uiowa.edu/ips/Meetings/Barcelona04.htm  

July 18–22, 2004  
International Neuro-Ophthalmology Society (INOS)  
Geneva, Switzerland  
http://www.symporg.ch/inos  
Contact: inos@symporg.ch