

Successive yet distinct episodes of isolated ophthalmoplegia associated with anti-GQ1b antibody

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Recurrent episodes of the Miller Fisher syndrome (MFS) are uncommon.¹ Furthermore, isolated internal ophthalmoplegia is rare in MFS.^{2,3} We report a patient who presented first with internal/external ophthalmoplegia, then 7 years later with an isolated internal ophthalmoplegia associated with elevated anti-GQ1b IgG antibodies and confirmed *Campylobacter jejuni* enteritis.

Case report. A 20-year-old Latino man first presented to an outside neurology group with double vision, photophobia, and ataxia following a bout of diarrhea 2 days prior to symptom onset. On examination there were limited extraocular movements, dilated, non-reactive pupils, impaired vibratory sense of the distal extremities, and normal reflexes. After unremarkable brain imaging and spinal fluid results, the patient was diagnosed with atypical MFS. No treatment was initiated and symptoms resolved over the course of 3 months.

At age 27 years he presented again with the gradual onset of double vision, photophobia, and paresthesias of the distal extremities 2 days after another bout of diarrhea. On examination, 4 days after the onset of visual symptoms, the patient was alert with normal cognition. His pupils were dilated at 7 mm, nonreactive to light or accommodation. Ocular motility was normal. His corrected visual acuity was 20/30 in the right eye and 20/25 in the left. Instillation of pilocarpine 1% induced bilateral miosis. The remainder of his cranial nerves were normal as was his motor and sensory examination. There were no signs of cerebellar dysfunction and his deep tendon reflexes were normal.

MRI of the brain and orbits with contrast was unremarkable. Lumbar puncture on day 5 after onset of symptoms demonstrated no white blood cells and a protein level of 21 mg/dL. A lumbar puncture repeated 10 days after symptom onset remained unremarkable. There were no oligoclonal bands detected in the CSF. Detailed nerve conduction studies and EMG were unremarkable. The Venereal Disease Research Laboratory test, Lyme serologies, and HIV screening tests were negative. The erythrocyte sedimentation rate, leukocyte count, and angiotensin converting enzyme studies were normal. An ELISA (Focus Diagnostics) showed an elevated serum anti-GQ1b IgG antibody titer of 1:400 (normal <1:100). An ELISA titer sent to Focus Diagnostics for serum *C. jejuni* antibody was also elevated at 3.5 (normal < 2). On day 18 after symptom onset a 3-day course of IVIg was initiated. Examination on day 19 demonstrated minimal reactivity to light of the right pupil.

Discussion. Our patient is at least the fifth report of isolated internal ophthalmoplegia associated with a positive anti-GQ1b antibody. Although a previous report described a patient with two episodes of MFS followed by an episode of Bickerstaff's brainstem encephalitis,⁴ as far as we know, this is the first report detailing the recurrence of an atypical Miller Fisher syndrome associated with elevated titers of anti-GQ1b IgG antibody and serologic evidence of *C. jejuni* enteritis.

This patient had double vision at his second presentation, but did not have objective external ophthalmoplegia; the subjective

complaint of double vision may reflect pupillary abnormalities, as noted in other patients with isolated internal ophthalmoplegia.^{2,4} GQ1b is a tetrasialoganglioside cell surface molecule found within human central and peripheral nervous systems. Serum IgG antibody against GQ1b is very closely associated with MFS, Guillain Barré syndrome with ophthalmoplegia, acute ophthalmoparesis without ataxia,⁵ and also found among those with isolated pupillary areflexia with limited or no external ophthalmoplegia.^{2,3} Over 90% of patients with MFS and GBS with ophthalmoplegia have an elevated serum anti-GQ1b antibody (with a broad range of positive titers) and this test has high specificity for the two diseases.⁵ Murine monoclonal anti-GQ1b antibody strongly stains the paranodal regions of the extramedullary portion of human oculomotor, trochlear, and abducens nerves and weakly stains the deep cerebellar nuclei.⁵ It has been hypothesized that there is also an enrichment of the GQ1b ganglioside in the ciliary ganglion leading to presentations of pupillary areflexia.²

C. jejuni enteritis is a frequent antecedent pathogen in both GBS/MFS with a recent study demonstrating 18% of patients with MFS having seropositivity for *C. jejuni*.⁶ Anti-GQ1b antibody cross-reacts with the lipopolysaccharide epitope on *C. jejuni*.⁷ This has led to the hypothesis that the anti-GQ1b antibody exerts its immunopathologic effect through molecular mimicry between *C. jejuni* and specific neural tissue, and may involve direct inhibition of neuromuscular transmission, antibody dependent complement activation, or inflammatory demyelination.

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Vascular dysplasia in neurofibromatosis type 2

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Neurofibromatosis type 1 (NF1) and 2 (NF2) are autosomal dominant disorders characterized by dysplasia in tissues of mesodermal and neuro-ectodermal origin. NF1 is associated with pigmented cutaneous lesions, neurofibromas, and other systemic

features including pheochromocytoma, scoliosis, and epilepsy.¹ An important cause of morbidity and mortality is an associated vasculopathy causing stenosis, occlusion, aneurysm, or arteriovenous fistula formation.² Patients with NF2 have few cutaneous lesions but a strong propensity to develop multiple tumors of the CNS, particularly bilateral vestibular schwannomas (VS).³ Systemic features are rare and vasculopathy is not known to be a manifestation of NF2. We report a case of intracerebral vascular dysplasia leading to left middle cerebral artery (MCA) infarction in a patient with molecularly confirmed NF2.

Case report. An 18-year-old right-handed woman was diagnosed clinically with NF2 in another institution. On presentation at age 11, she had a right trigeminal neuropathy, right eye proptosis, bilateral papilledema, and partial right third nerve palsy. There were no motor or sensory deficits in the extremities. MRI brain and spinal cord revealed bilateral VS, multiple intracranial meningiomas, posterior meningioma at T1, and multiple schwannomas along lumbar nerve roots. The patient's mother had clinical NF2 (unconfirmed molecularly) and died at age 35 following spinal surgery. At the time of death, she had bilateral VS, three other brain tumors, and two spinal tumors. There was no family history of another affected relative.

Our patient underwent surgical excision of a cribriform plate and right orbital meningioma with subsequent insertion of a ventriculoperitoneal shunt. A postoperative brain CT shows bilateral VS, calcified right sphenoid wing meningioma, falcine meningioma, and postoperative frontal gliotic change (figure, A).

In August 2003, she presented with stuttering onset of expressive dysphasia and right hemiparesis. There were no known vascular risk factors. She was in sinus rhythm, was normotensive, and had a normal cardiovascular examination. She had a global aphasia, right homonymous hemianopia, right facial weakness, and a dense right hemiparesis. Diffusion-weighted MRI revealed acute infarction in the left MCA territory (figure, B). MR angiography (MRA) of head and neck showed asymmetry with narrowing and irregularity of the left MCA (figure, C). Four-vessel angiogram revealed a diffusely dysplastic left MCA extending from close to the origin of the M1 segment and involving several insular branches, one of which was markedly stenosed (figure, D). There was no other evidence of intracranial stenosis or vascular abnormality. A complete thrombophilia and vasculitic screen, transthoracic echocardiogram, and Holter monitor were normal. She was treated with warfarin, low dose aspirin, and statin therapy. Clinically there was moderate recovery of right upper and lower limb function, but a moderately severe aphasia persisted. Follow-up MRA at 1 year showed persistent left MCA stenosis.

A previously described splice site mutation, 600-2A>G,⁴ was identified in exon 7 of the NF2 gene confirming the diagnosis of NF2.

Discussion. Vascular dysplasia has not been reported in association with NF2 although some vascular abnormalities have been described in patients with NF2⁵ and retinal hamartomas are a recognized feature. The true incidence of vascular dysplasia in NF1 is not known and many patients may be asymptomatic. As the incidence of NF2 is approximately one tenth that of NF1 (1:33,000 to 1:3,000),^{1,3} the association may not have been appreciated because of its rarity.

Genotype-phenotype correlations have been described for NF2-associated intracranial meningiomas, spinal, and peripheral nerve tumors.⁶ Missense and splice-site mutations (as in our patient) have been associated with fewer tumors than nonsense or frame-shift mutations but this may depend on the location of the splice-site mutation within the gene, 3' mutations causing less severe disease than 5'.

Although the vasculopathy of NF1 is incompletely understood, it may be due to failure to regulate intimal proliferation. This is suggested pathologically by intimal proliferation and hyperplasia resulting in luminal stenosis.² This case now raises the question of a link between the vasculopathy of NF1 and NF2. NF2 is caused by a mutation in the merlin protein located on chromosome 22q12.2. Merlin functions as a tumor suppressor gene and regulates cell growth and proliferation.⁷ Similar to NF1, failure of merlin to control intimal proliferation in the vascular tree may lead to hyperplasia and vessel occlusion.

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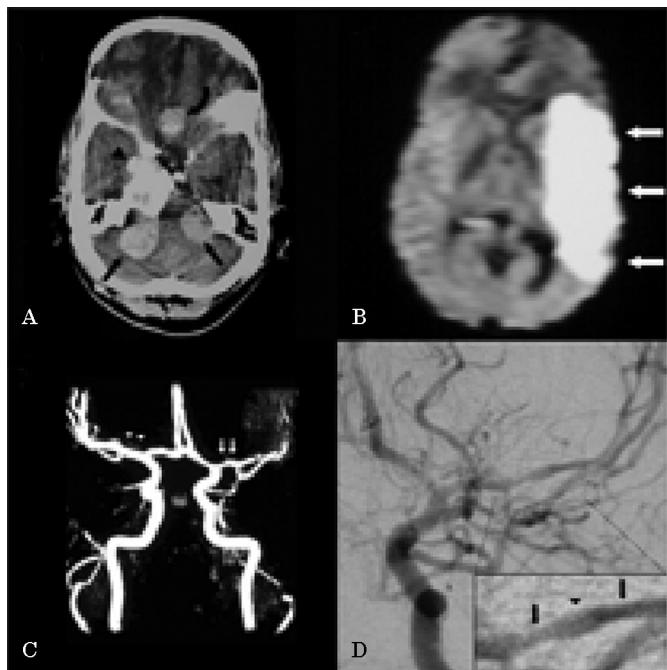


Figure. (A) Axial brain CT showing bilateral vestibular schwannomas (arrows), calcified right sphenoid wing meningioma (arrowhead), falcine meningioma (curved arrow), and postoperative frontal gliotic change. (B) Axial, diffusion-weighted image showing diffuse high signal in the left middle cerebral artery (MCA) territory consistent with acute infarction. (C) Asymmetry with focal narrowing of the left MCA (arrows) on MRA. (D) Left carotid angiogram showing focal stenoses (arrows) and interstenotic dilatation (arrowheads) of left MCA.

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Encephalopathy in a patient with previous malignancy but normal brain imaging

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A 61-year-old man presented following two generalized tonic clonic seizures. For 2 weeks prior to admission he had had occipital headaches. The patient's family had noticed a change in his personality with confusion, memory impairment, and unsteadiness when walking.

The patient had a history of non-small cell lung cancer (stage IV) diagnosed 2 years previously. He had completed three courses of chemotherapy with regimes of gemcitabine and carboplatin, docetaxel, and carboplatin with a clinical trial drug TZT1027. His most recent course was with oral gefitinib (Iressa). This was discontinued 6 months previously because of a persistent urticarial rash. He had no other significant past medical history.

On admission the patient was oriented in time and place. His speech was normal. He was afebrile. No focal neurologic deficits were noted. At the admitting hospital routine hematologic and biochemical investigations were normal. Liver transaminases were slightly elevated. A noncontrast enhanced CT scan of brain was reported as showing small vessel ischemic change. Lumbar puncture examination was normal. An initial diagnosis of viral encephalitis was considered and the patient was commenced on acyclovir and valproic acid.

Over a period of 2 days the patient's condition gradually deteriorated. He became disorientated and drowsy. On examination he had broken saccadic eye movements and exhibited perseveration. No focal neurologic deficits were found on limb examination; plantar responses were flexor. He had a right pleural effusion. A contrast enhanced MRI scan was reported as showing a few areas of high signal intensity on T2-weighted images consistent with small vessel ischemic change. FLAIR and gradient echo sequences were not performed. An EEG record showed diffuse slow wave activity. Multiple CSF examinations were performed and were negative for cytology, viral PCR, tuberculosis PCR, and ammonium. Autoimmune and vasculitic screens were negative.

As a result of continued clinical deterioration a repeat MRI scan was performed 2 weeks after the initial scan. This revealed innumerable small high signal foci in the brain parenchyma on T2-weighted axial images. There was no mass effect or generalized edema (figure). Axial T1-weighted images with gadolinium contrast showed only vague enhancement within a few lesions. Coronal gradient echo images showed focal signal change in two lesions indicating hemorrhagic change.

A diagnosis of carcinomatous encephalitis was made based on the clinical picture and MRI appearances. The differential diagnosis of these lesions would have included miliary infections such as tuberculosis but there was no clinical or laboratory evidence of infection. The patient's condition continued to deteriorate and he was transferred to a hospice for palliative care. The patient died 1 month after initial presentation.

Discussion. The term carcinomatous encephalitis (miliary metastases) was used first by Madow and Alpers in 1951¹ to describe the appearance of numerous tiny perivascular nodules consisting of tumor cells originating from a distant primary neoplasm, usually lung. The original patients presented had a combination of an organic mental syndrome and hemiparesis.¹ Subsequent reports have recognized seizures,² speech difficulties,³ and gait abnormalities⁴ to be early presenting features of the condition.

It is estimated that between 20 and 30% of all patients with a systemic carcinoma have brain metastases at time of death.⁵ The usual appearance of cerebral metastases is of single or multiple intra-axial masses at or near the gray white matter junction with surrounding edema. The lesions of carcinomatous encephalitis typically occur in perivascular spaces and do not cause surrounding edema or mass effect.^{3,4}

Previous reports on carcinomatous encephalitis have been

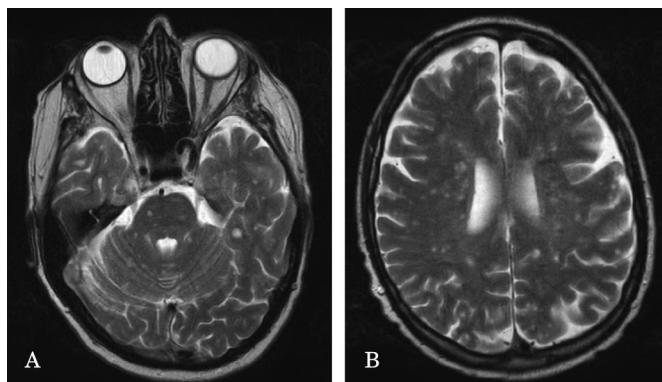


Figure. (A, B) Axial T2-weighted images showing multiple high signal foci in the brain parenchyma of the supra and infratentorial compartments including the brainstem. Note the lack of mass effect or edema.

scant in the medical literature and those containing MR imaging have been inconsistent, suggesting the lesions are contrast enhancing,^{3,6} non-contrast enhancing,² calcified,⁷ or possibly hemorrhagic.⁴ The prognosis for carcinomatous encephalitis is considered to be poor with published figures from diagnosis to death ranging from 14 days⁵ to 7 months.² However, the poor prognosis may be in part due to the prolonged delay in diagnosis because of over-reliance on currently available imaging techniques. In this case metastatic brain disease was always the most likely clinical diagnosis despite the unremarkable initial MRI scan although the first scan was incomplete, not including FLAIR and gradient echo sequences. There are currently no published data on how often imaging should be repeated to identify carcinomatous encephalitis in the presence of strong clinical suspicion.

Previously published individual trials of brain irradiation did not affect outcome³ but this may be due to delivery of the treatment late in the clinical course. Further studies are required to establish whether irradiation therapy administered based on strong clinical suspicion alone, even in the presence of unremarkable imaging, may prolong patient survival.

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Acute multifocal CNS demyelination as first presentation of systemic malignancy

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We present a patient with adenocarcinoma of the lung, without CNS metastases, who developed progressive quadraparesis like that seen in the paraneoplastic syndrome acute necrotic myelopathy.¹ Pathologic examination revealed only areas of brainstem and spinal cord demyelination resembling the acute lesions of multiple sclerosis (MS).

Case report. A 66-year-old man was hospitalized after 4 weeks of persistent cough and 10 days of weakness and paresthesias of the legs. Over the next 5 days, his weakness progressed to paralysis of all extremities, dysphagia, and respiratory failure. He developed bilateral Babinski signs. Cognition and vision were unaffected and the sensory examination remained normal despite paresthesias. Chest CT scan revealed a hilar mass and abnormal masses in the liver and an adrenal gland, but biopsies of the hilar mass and the liver nodule were nondiagnostic. MRI of the brain and cervical spinal cord showed increased T2 signal in the medulla, extending into the upper cervical cord and a separate focus of T2 hyperintensity in the spinal cord at the level of the third thoracic vertebra, without abnormal enhancement (figure, A). CSF had 10 leukocytes/ μ L (99% mononuclear), 8 erythrocytes/ μ L, protein 42 mg/dL, glucose 78 mg/dL, no oligoclonal bands, negative cytology, and negative PCR testing for herpes simplex and varicella zoster viruses. An IgG index was not determined. Assays for the following serum antibodies associated with paraneoplastic syndromes were negative: Anti-Hu; Anti-Yo; anti-neuronal type 1, 2, and 3; Purkinje cell cytoplasmic type 1, 2, and Tr; anti-amphiphysin; anti-CRMP-5 IgG; striational antibody; anti-calcium channel P/Q type and N-type; and anti-acetylcholine receptor.

Methylprednisolone 500 mg daily for 8 days failed to improve the patient's condition. He died on the 11th hospital day after ventilatory support was withdrawn at his request.

Autopsy revealed an adenocarcinoma arising from the right mainstem bronchial mucosa, with spread to hilar nodes and to the right adrenal. The tumor showed no features of neuroendocrine differentiation by light microscopy nor did it stain for neural cell adhesion molecule (CD-56) or chromogranin. Neuropathologic examination disclosed three separate well-circumscribed lesions in the cord and brainstem with the largest, 1.2 \times 1.0 cm, encompassing the floor of the medulla and extending into the basis pontis (figure, B). Thoracic and lumbar cord demyelinative plaques were wedge-shaped, adjacent to pial surface, abutted the central canal, and showed symmetry across the ventral sulcus, patterns identical to those classically seen in MS. These sharply demarcated, noncavitated, non-necrotic lesions demonstrated sheets of CD68+ macrophages containing Luxol fast blue positive debris, indicating acute myelin breakdown. Swollen axons and perivascular CD3+ T cell lymphocytic cuffing were also frequent. Stains for herpes simplex virus, cytomegalovirus, and Epstein Barr virus were negative. Metastatic tumor, neuronal degeneration, small perivenular demyelinative lesions, optic chiasm demyelination, or remote MS plaques were not identified in the CNS.

Discussion. Our patient developed multiple acute demyelinating lesions in the brainstem and spinal cord as a presenting sign of adenocarcinoma of the lung. The pathologic findings, including subependymal and subpial involvement, symmetric demyelinative lesions crossing the spinal cord ventral sulcus, and perivascular inflammation, more closely resemble those of an acute episode of MS than other demyelinating syndromes. The lesions were not as widespread as is typical for the related condition acute disseminated encephalomyelitis.

Our patient rapidly progressed to quadraparesis, had prominent involvement of the spinal cord, a poor response to corticosteroid therapy, and a carcinoma of the lung. These features are similar to the rare but well-documented paraneoplastic syndrome, acute necrotic myelopathy.¹ However, the pathologic examination revealed no evidence of necrosis in the CNS. A related condition, neuromyelitis optica, was further excluded by the absence of optic nerve lesions.

Single focal tumor-like areas of cerebral demyelination have been described as a paraneoplastic manifestation of seminoma (two cases), CML (one case), and non-Hodgkin lymphoma (one case).²⁻⁴ A similar

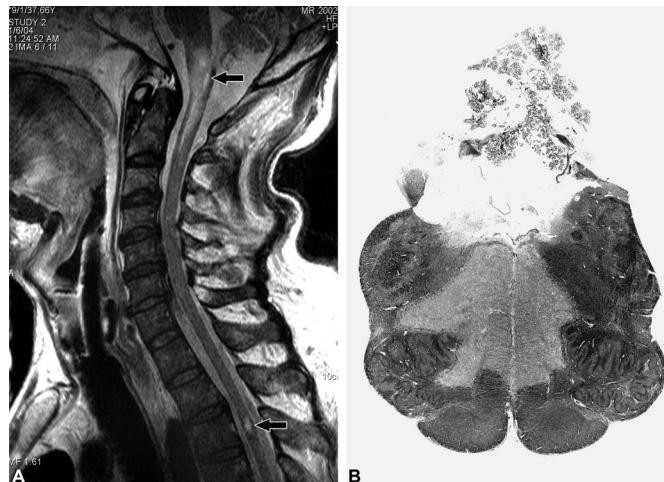


Figure. (A) T2-weighted gradient echo MR image (repetition time 500, echo time 19, flip angle 20°) demonstrating two of the patient's three distinct, hyperintense lesions involving the lower brainstem and upper thoracic cord (arrows). (B) Whole mount section from the medulla stained for myelin showing a subependymal sharply demarcated demyelinative plaque involving the floor of the fourth ventricle. Luxol fast blue, 3x.

focal tumor-like area of demyelination may be a "sentinel lesion" for primary CNS B-cell lymphoma.⁵ Other cases with demyelination in association with systemic neoplasms have also displayed significant neuronal degeneration and were most consistent with the syndrome of anti-Hu mediated limbic encephalitis.⁶

Although we conducted an extensive search for antibodies associated with paraneoplastic neurologic syndromes, we found none. No antibody is known to be associated with single focal acute demyelinating lesions or paraneoplastic necrotizing myelopathy, but anti-CRMP-5 antibodies have been found in a paraneoplastic syndrome resembling neuromyelitis optica.⁷ We cannot establish a direct cause-and-effect relationship between the acute MS-like syndrome and the systemic cancer in our single patient, but the temporal link was striking.

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Systemic autoantibodies against discrete inner ear compartments in bilateral vestibular loss

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Thirty to 50% of cases of bilateral vestibular failure are idiopathic.¹ However, an autoimmune cause has been suggested in some cases with bilateral idiopathic vestibular failure (BIVF).²⁻⁴ The pathogenesis in autoimmune inner ear disease (AIED) is poorly understood, and no specific diagnostic test is available. The western blot technique is useful in diagnosing AIED, although the antigen used is often heat shock protein-70 (hsp-70) from bovine kidney tissue and therefore lacks ear specificity.

Case reports. Two patients were admitted for investigations. This project was approved by the Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery (Queen Square, London, UK). Patient A was a 57-year-old man who had a 3-year history of recurrent episodes of severe vertigo and progressive unsteadiness. Examination revealed an unsteady ataxic gait and a bilateral positive head-thrust test. No nystagmus could be elicited during caloric irrigation (30 and 44 °C) or with rotational steps of 60°/s. CSF analysis showed a protein concentration of 0.43 g/L and oligoclonal bands in the CSF with few matched bands in the serum (figure). Patient B was a 51-year-old woman who presented with a history of a single acute episode of vertigo and sickness. In this patient, the vertigo gradually resolved, but a severe imbalance remained. Clinical examination showed an unsteady gait and a bilateral positive head-thrust test. There was total absence of nystagmic response to rotational steps of 80°/s. In both patients, antineuronal antibodies were negative and brain MRI and pure tone audiogram were normal (for additional information see table E-1 on the *Neurology* Web site at www.neurology.org).

Antibodies in sera were studied by using the western blot technique. Discrete compartments of inner ear tissue from guinea pigs were used as antigen (organ of Corti, stria vascularis, three semicircular canals with the ampullary tissue, utricle, and endolymphatic sac).⁵ Renal medulla and brain were used as control tissues. Extracted antigens were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The same amounts of protein from the various tissues were loaded on each gel to enable semiquantitative evaluation. The filters were incubated overnight with sera (diluted 1:1,000) followed by incubation with anti-human IgG secondary antibody. Detection was performed with enhanced chemiluminescent substrate.

Results. Both patients had ear-specific antibodies against proteins migrating at 188, 49, and 17 kd (see the figure). In addition, both patients had antibodies against a 68-kd kidney protein with a weak corresponding band in the whole-ear tissue preparation. This band may represent hsp-70.^{6,7} Serum from two subjects (one with congenital profound sensorineural hearing loss with bilateral vestibular hypofunction and one with noise-induced sensorineural hearing loss) served as controls and had no ear-specific antibodies. The oligoclonal bands in CSF present in Patient A prompted us to investigate the presence of ear-specific antibodies in CSF. Interestingly, when incubated with CSF (diluted 1:1,000), some weak bands corresponding to those found in serum were found.

Discussion. In the current study, we used discrete inner ear tissues as antigens to investigate patients with BIVF. The bands in Patient A were present only in parts containing secretory epithelia. It is therefore tempting to conclude that the antibodies are directed against proteins present only in secretory epithelia, leading to loss of function in this particular cell type. In Patient B, the

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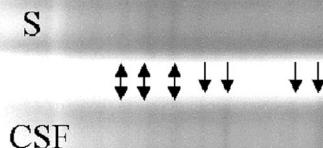


Figure. Isoelectric focusing used to detect oligoclonal bands of IgG in serum and CSF from Patient A. Double arrow = matched bands; single arrow = unmatched band.

reaction is not only present in the parts containing secretory epithelia but also in the purely sensory epithelial tissue preparation (i.e., the organ of Corti) (see the figure). The absence of cochlear symptoms in this patient could be explained if the identified protein were, under normal conditions, not easily reached by the immune system.

Our findings are in agreement with a previous immunofluorescent study in which sera in 8 of 12 patients with BIVF were shown to have antibodies mainly against the ampullary tissue and the semicircular canals.² Interestingly, using the western blot technique, the same group of researchers has also shown reaction with a CNS-related 45-kd rat protein in serum from a patient with suggested sympathetic vestibulopathy.³

In the current study, the two patients with BIVF were shown to have three ear-specific autoantibodies in common. This may indicate similar pathoetiology despite different clinical presentation. The presence of autoantibodies does not prove that they are the underlying cause of vestibular loss. However, the antigens found in this study may be more specific for BIVF than kidney hsp-70, which is the antigen often used to support the diagnosis of AIED.

As the western blot technique provides the possibility of identifying the specific protein responsible for autoantibody production, it may be a useful diagnostic tool for BIVF.

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Infarction of the central cerebellar arbor vitae and transient loss of spatial orientation

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Case report. A 45-year-old man traveling by train had acute severe pain in the right shoulder after lifting a heavy suitcase, followed by 15 seconds of non-motion-directed vertigo. He sat down and felt well, except for minor persisting pain in the shoulder. After a symptom-free interval of 4 hours, he reported a sudden transient loss of spatial orientation and a feeling of being shaken in an airplane during severe turbulence. Apparently he had involuntarily moved on his seat, prompting startled looks from fellow passengers. During this episode, he had no diplopia, nausea, or visual disturbances. After a few minutes, he recovered completely apart from persisting pain in the right shoulder and neck. Orthopedic consultation and neurologic examination 5 hours after onset of symptoms were normal, at which time the pain was subsiding. Electronystagmography was normal except for a minimally decreased downward optokinetic nystagmus.

Extracranial Doppler/duplex sonography and MR angiography confirmed a dissection of the right vertebral artery as suspected from the acute pain syndrome. Diffusion-weighted MRI, the apparent diffusion coefficient, and fluid-attenuated inversion recovery studies revealed a small acute infarction of 2 mm in diameter in the center of the cerebellar vermis. T2-weighted images demonstrated a hematoma of the wall and missing flow void in the V5 segment of the right vertebral artery. By means of perfusion-weighted MRI, the vascular territory affected by the dissection could be identified: Time-to-peak maps demonstrated a late arrival of the contrast medium in the complete right posterior inferior cerebellar artery (PICA) territory¹ (figure, A). Ischemia was considered of arterioarterial embolic origin from the dissected vertebral artery into the most distal PICA territory of the vermis, where emboli were trapped in an area of very low perfusion.

Discussion. The fastigial nuclei close to the medullary center of the vermis integrate afferences from the vermiciform cortices, the vestibular nuclei, and the accessory olives and have efferences via the lower cerebellar peduncles back to the vestibular nuclei. They are the major cerebellar relay mediating inhibition on the vestibular system. The acute ischemic lesion observed in this patient fits both the fastigial nucleus and its afferent tracts^{2,3} from the vermiciform cortex (VII) (see figure, B).

A history of sudden-onset vertigo associated with a loss of spatial orientation, though transient and nondirected, is indicative of acute cerebellar stroke. By clinical presentation, cerebellar signs may already have improved. Although the lesion site may vary, the syndrome is underestimated owing to often scant history taking in emergency room settings. If vertigo is combined with characteristic pain, dissection of the vertebral artery is highly suggestive, and MRI should include isotropic diffusion weighting with particular attention to midline structures, which might be misinterpreted as artifacts. Spatial orientation seems to be integrated in the center of the arbor vitae.

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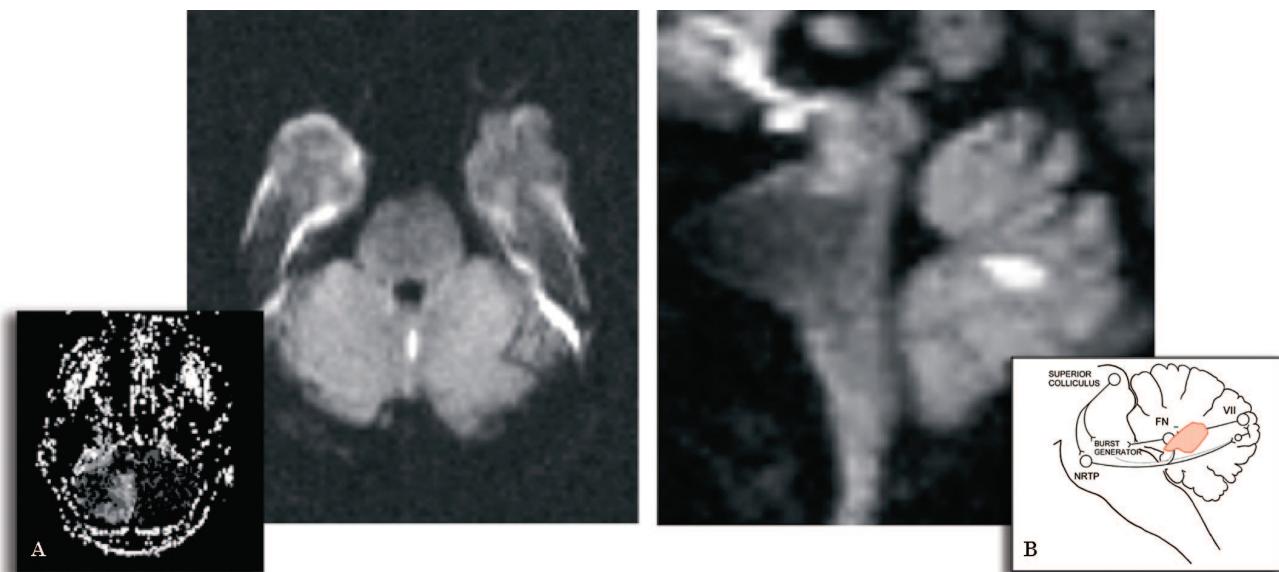


Figure. (A) Infarction in the center of the cerebellar vermis (diffusion-weighted imaging, 6 hours after initial symptoms). (Inset) Perfusion-weighted imaging indicating delayed bolus arrival in the right posterior inferior cerebellar artery territory due to a dissection of the right vertebral artery. (B) Diffusion-weighted MRI of the lesion in the center of the cerebellar vermis (sagittal projection) vs schematics² (rhesus monkey) of the fastigial nucleus (FN) integration and the critical cerebellar projection area (VII). The corresponding area of the infarction is shown in the schematic drawing (inset). Further components²: nucleus reticularis tegmenti pontis (NRTP), saccadic burst generator.

Isolated oculomotor palsy following minor head trauma

Richard L. Levy, MD; Craig E. Geist, MD; and Neil R. Miller, MD

Case report. A 54-year-old woman with an unremarkable medical history was in a minor motor vehicle collision resulting in airbag deployment. She reported loss of consciousness lasting a few seconds. She had no bruises or lacerations, but she immediately noted drooping of her left eyelid and double vision when she elevated the lid. She was taken to a local hospital, where she had an isolated, complete left oculomotor nerve palsy with a nonreactive pupil (figure). CT, MRI, and MR angiography were all normal (see figure E-1 on the *Neurology* Web site; go to www.neurology.org).

Over the next 6 weeks, the patient experienced mild improvement in ptosis, pupillary function, and ocular motility, but because of persistent diplopia and ptosis, she presented to the Wilmer Eye Clinic. On examination, the patient had normal visual sensory function, except for reduced accommodation on the left. The pupils were equal in size, but the left pupil was less reactive than the right pupil to both light and near stimulation. There was a moderate left ptosis that improved on attempted down-gaze and right-gaze. The right eye moved fully. The left eye had moderately reduced adduction, elevation, and depression. There was intorsion of the left eye on attempted down-gaze to the left. In primary position, the patient had a 45-prism-diopter exotropia and a small left hypotropia. Corneal and facial sensation were equal and normal bilaterally. There was no proptosis or enophthalmos.

Because of the history of relatively mild trauma, we were concerned about an underlying vascular lesion. Accordingly, the patient underwent a four-vessel digital subtraction angiogram. The study showed no intracranial arterial or venous abnormalities. No further testing was performed.

At the last follow-up visit, 5 months after the accident, the patient reported only intermittent diplopia. She had a mild left ptosis that improved on down-gaze and left-gaze. The left pupil now reacted well to light and near stimulation but slightly less so than the right pupil, and on slit-lamp examination, there was a relative hypokinesis of the superior aspect of the pupillary margin. The left eye could now adduct, and both elevation and depression were markedly improved although still limited. There was now an 18-prism-diopter exotropia in primary gaze.

Discussion. Third nerve palsies following blunt head trauma are common. The trauma required to damage the oculomotor nerve usually is extensive and associated with loss of consciousness, basilar skull fracture, or subarachnoid hemorrhage. Thus, traumatic third nerve palsies usually occur in association with other neurologic deficits.¹ In rare cases, blunt trauma can cause an isolated third nerve palsy, but even in this setting, the trauma is generally severe. For this reason, a third nerve palsy that occurs after mild trauma should raise concern that there is an underlying lesion that is compressing, stretching, or infiltrating the oculomotor nerve, predisposing it to dysfunction following an

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the July 12 issue to find the title link for this article.

otherwise inconsequential injury. In some patients, a third nerve palsy after minor head trauma is the presenting sign of a posterior circulation aneurysm²⁻⁴ or a basal intracranial tumor.⁵ In such cases, the trauma is insufficient to cause fracture or loss of consciousness. Although our patient reported a transient loss of consciousness, we still consider her trauma minor, given the mechanism of injury and the lack of fracture or associated neurologic deficits.

True traumatic third nerve palsies may be caused by damage to the nerve at any point along its path, from the brainstem to the orbit.⁶ In one report, a 39-year-old woman developed a left partial, pupil-involving third nerve palsy immediately following a car accident in which she experienced a brief loss of consciousness.⁷ MRI revealed no abnormalities except on gradient echo T2-weighted images that showed a signal hypointensity consistent with hemorrhage at the midbrain exit site of the oculomotor nerve. The authors concluded that gradient echo MR sequences may be more sensitive than other sequences in detecting this phenomenon. Our patient underwent MRI that included gradient echo images, but no abnormalities of the third nerve were identified.

Because our patient developed a complete third nerve palsy with involvement of the pupil after relatively minor trauma, followed by partial recovery and secondary aberrant regeneration, she underwent not only noninvasive imaging studies (CT, MRI, MR angiography) but a subsequent catheter angiogram. The lack of findings on these studies indicates that it is possible to have a severe oculomotor nerve palsy following relatively minor trauma without associated morbidity. As this is a rare event, an underlying vascular or other abnormality should still be investigated. In addition, as not all noninvasive studies provide optimal images, noninvasive imaging that is suboptimal should be repeated before catheter angiography is performed.

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Figure. Appearance of patient on initial presentation. Note complete third nerve palsy with pupil involvement.

Delayed oculomotor nerve palsy after bilateral cervical zoster in an immunocompetent patient

Yuval Karmon, MD; and Natan Gadoth, PhD

Case report. A 54-year-old Israeli-Arab man noticed drooping of the left eyelid, which evolved over 4 days prior to his admission (PTA) to the Department of Neurology at the Meir General Hospital. Left retro-orbital pain appeared 2 days later; on the day of admission, vertical diplopia was noticed.

Three weeks PTA, he experienced excruciating neck pain more on the left side and also over the right occipital scalp. A few days later, he noticed right posterior cervical skin eruption in the form of small clear blisters, for which he was given antibiotics. The eruption resolved in 2 weeks, yet neck pain persisted.

On admission, he was afebrile with few hyperpigmented tender scars present mainly over the right and, to a lesser extent, over the left posterior aspect of the neck, which was supple. The neurologic examination revealed isolated left oculomotor nerve palsy with pupillary sparing. However, on the following morning, left pupillary dilatation with sluggish reaction to light was noticed. Brain CT, computed cranial angiography, and gadolinium-enhanced MRI were all normal. The clear and sterile CSF was under normal opening pressure and contained 150 mononuclear cells/mL³, which were classified as T lymphocytes by immunophenotyping. No malignant cells were detected. The protein was elevated (66 mg%), and the glucose level was normal. Complete blood counts, blood chemistry, protein and immuno-electrophoresis, serologic tests for antinuclear antibodies, complement, perinuclear antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic-ANCA, lupus anticoagulant, anticardiolipin, angiotensin-converting enzyme, and antibodies to acetylcholine receptor were normal or negative. Serologic tests for various infectious agents including HIV were negative. Chest radiographs, abdominal sonography, isotope bone scan, and tumor markers were all negative. PCR on CSF was positive for varicella zoster virus (VZV) and negative for herpes simplex virus 1 and 2. IV Acyclovir was given for 21 days; pain and diplopia resolved completely over 2 weeks, and ptosis resolved completely 1 month later.

Discussion. There are two outstanding clinical features in our patient. The first is the bilateral distribution of herpes zoster (HZ), which is unusually encountered in immunocompetent subjects,¹ and the second is the fact that delayed oculomotor palsy is a known complication of ophthalmic zoster only.

CNS lesions including cranial neuropathies that are remote from the site of the HZ eruption were considered to be caused by a

vascular-ischemic mechanism.² The blood supply of all cranial nerves stems from the carotid system through small branches that supply groups of two or three cranial nerves.³ It was postulated that there are anatomic pathways by which VZV could spread from trigeminal skin afferents to the walls of pial and dural blood vessels of the carotid system.⁴ The presence of such pathways was demonstrated in the cat model.⁵ Those observations sufficiently explain oculomotor neuropathy following ophthalmic zoster but cannot account for oculomotor palsy following cervical zoster, which has never been reported so far.

The occurrence of brainstem strokes following ophthalmic, maxillary, and cervical HZ suggests the presence of an anatomic network connecting the trigeminal and cervical ganglionic neurons with the vertebrobasilar system.^{6,7} Indeed, bilateral removal of the C1 to C3 dorsal root ganglia in cats results in reduced concentration of substance P in the vertebobasilar system, which is prevented by prior removal of both trigeminal ganglia.⁴

Thus, it can be stated that the cranial neuropathy in our patient is additional clinical evidence of the presence of these anatomic neurovascular connections.

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Life-threatening acute pancreatitis associated with interferon beta-1a treatment in multiple sclerosis

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The treatment goal in patients with relapsing-remitting multiple sclerosis (RR-MS) is to reduce the frequency and severity of relapses and to prevent or postpone the development of disability. Large trials have demonstrated that interferon beta-1a (IFN β -1a), IFN β -1b, and glatiramer acetate partially meet this purpose.¹ The approved drugs are well tolerated with largely transient adverse effects. Pancreatitis is not mentioned as an adverse effect in the current Summaries of Product Characteristics for IFN β -1a. However, acute pancreatitis has been associated with IFN α -2b treatment.² We report a case in which a life-threatening acute pancreatitis developed 8 weeks after the initiation of treatment with IFN β -1a for RR-MS.

Case report. A healthy 53-year-old man on no concurrent medication was diagnosed with MS. He started with IFN β -1a (Rebif) 22 μ g subcutaneously three times weekly 8 weeks after diagnosis. Initially, he experienced minor injection site reactions and flu-like symptoms. However, 8 weeks later, he developed symptoms of an acute pancreatitis. The serum amylase concentration was $>3,000$ U/L (reference interval 70 to 300 U/L). MR cholangiopancreatography and ultrasonography showed no signs

of gallstones. The common bile duct and the main pancreatic duct appeared normal. There were no signs of infections, hyperlipidemia, hypercalcemia, trauma, ischemic disease, or tumors. He had no history of alcohol abuse. Prior to IFN β -1a therapy, a hematologic and biochemical workup including γ -glutamyl transferase (13 U/L), alanine aminotransferase (14 U/L), and aspartate aminotransferase (23 U/L) were normal. He scored 3 of a maximum of 40 points in an Alcohol Use Disorders Identification Test (AUDIT)³ questionnaire interview.

Two days after hospitalization, he was transferred to intensive care. Abdominal and thoracic CT scans showed pancreatic necrosis and peripancreatic fluid collection. The IFN β -1a therapy was stopped after 4 days in hospital. After 3 weeks, changes in the clinical and biochemical variables indicated an infected pancreatic necrosis. Drainage was performed, using pigtail catheters percutaneously for 3 weeks. An exploratory laparotomy was done, comprising partial resection of the pancreas, splenectomy, and abdominal abscess drainage. Following this intervention, his condition gradually improved. He was transferred to rehabilitation after 12 weeks of hospitalization. Two weeks thereafter, he was readmitted with increasing pain in the upper abdomen. A new pancreatic abscess was identified and drained. Subsequently, a pancreatic fistula developed. Finally, the main pancreatic duct was stented, and his condition improved. The stent was later removed.

A neurologic follow-up 4 months later showed a stable situation without new clinical MS-related disease activity. He was go-

ing back to work and was not prepared to start any new kind of immunomodulatory treatment. A rechallenge with IFN β -1a was considered inappropriate for ethical reasons.

Discussion. The underlying causes of acute pancreatitis include obstruction of the pancreatic duct outlet, abdominal trauma, metabolic abnormalities comprising hyperlipidemia and hypercalcemia, inherited conditions, infections, vascular abnormalities, iatrogenic conditions, and toxins. The most common causes are gallstone disease and ethanol abuse.⁴ The drugs most often implicated are azathioprine, mercaptopurine, valproic acid, didanosin, estrogens, metronidazole, tetracyclines, and rifampicin.⁵

The general disease history of our patient and his family did not include any specific risk factors for pancreatitis. His alcohol consumption was low, his AUDIT score putting him well below the validated cut-off of 8 that indicates a likelihood of hazardous or harmful alcohol consumption in men.³ He did not use any concomitant medication, and no signs of gallstone disease or other possible causes were detected.

Epidemiologic studies in Norway indicate an MS incidence rate of 5 per 100,000 per year,⁶ whereas the rate for acute pancreatitis⁴ is 30 to 40 per 100,000 per year. Thus, we cannot rule out that the appearance of a severe acute pancreatitis and the start of IFN β -1a therapy in a patient with MS can be a coincidence.

Up until February 18, 2005, the World Health Organization database of adverse drug reactions⁷ held a total of 45 reports on pancreatitis for IFN β -1a and 34 for IFN β -1b. The severity of these adverse effects is not reported. In total, this database contains about 3 million reported cases of suspected adverse drug reactions from >70 countries. However, as these reports in many cases represent only a suspicion of a relationship and might be based on a coincidence, no proof of causality can be made on the basis of these data.

As we were able to exclude other potential causes of acute pancreatitis, our case report strengthens the suspicion of a causal relationship between the administration of IFN β -1a and the de-

velopment of pancreatitis. However, the occurrence is obviously rare.

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Progressive cervical myelopathy secondary to chronic ventriculoperitoneal CSF overshunting

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CSF hypovolemia typically causes orthostatic headache with or without nonlocalizing symptoms such as neck pain, nausea, aural fullness, and dizziness.¹ Focal complications are rare and are usually secondary to subdural hematoma. We report findings from a patient with progressive cervical myelopathy associated with cord distortion due to dural thickening and tortuous venous dilation. Chronic CSF hypotension caused by excessive ventriculoperitoneal shunting seemed to be the primary etiology.

Case report. A 72-year-old woman presented for evaluation of an undiagnosed gait disorder. Twenty-seven years earlier she underwent right suboccipital craniectomy and ventriculoperitoneal shunt placement for a posterior fossa meningioma. There was no tumor recurrence or shunt malfunction. Four years earlier, she noted the insidious onset of right lower extremity spastic monoparesis. During the year prior to presentation, she developed bilateral leg and right arm weakness, left upper extremity numbness, and urinary urge incontinence. She denied headache, neck and shoulder pain, and orthostatic symptoms.

Examination revealed a moderately severe, right-predominant, asymmetric spastic quadripareisis with generalized hyperreflexia, bilateral extensor plantar responses, and mild vibratory and proprioceptive difficulties. There were neither segmental motor findings nor a sensory level. Her shunt valve depressed but filled extremely slowly.

Brain MRI (figure, A) demonstrated the shunt tip in the left frontal horn and postoperative changes involving the right cerebellum. The lateral ventricles were slit-like and there were bilateral subdural fluid collections and diffuse dural thickening and gadolinium enhancement consistent with intracranial hypotension secondary to CSF hypovolemia. These features were unchanged from an MRI performed 18 months earlier. There was no evidence of superficial siderosis. Lumbar puncture confirmed low opening

pressure (30 mm H₂O). The CSF was xanthochromic but acellular, total protein level was 189 mg/dL, and immunologic studies were negative. Serologic testing for medical causes for myelopathy was unrevealing.

Cervical spine MRI demonstrated cord distortion associated with dilated and tortuous dorsal vasculature. The spinal pachymeninges were diffusely thickened and enhanced with gadolinium; in some dorsal regions, the enhancement had a nodular appearance due to enlarged epidural veins (figure, B). There was no abnormal T2-weighted signal abnormality or enhancement within the cord. MR angiography of the cervical and upper thoracic spinal canal confirmed the presence of dilated epidural veins but did not detect a dural arteriovenous fistula (figure, C).

The patient was offered surgical intervention (shunt clamping with intracranial pressure monitoring) but declined. Nineteen months later, her hand weakness had progressed mildly but imaging abnormalities were unchanged.

Discussion. We hypothesize that the clinical findings are best explained by cord distortion and compression secondary to diffuse pachymeningeal thickening and venous dilation as a result of CSF hypovolemia from chronic overshunting. The protracted duration of overshunting may have obscured or prevented postural symptoms, which are not always present in cases of CSF hypovolemia from other causes. The spinal pachymeningeal abnormalities may represent an extension of the chronic dural sterile inflammation and thickening present in cranial dural biopsy specimens obtained in cases of CSF hypovolemia. We excluded the main primary cause for venous dilation, an occult dural arteriovenous fistula, by MR angiography; such a lesion would not explain CSF hypovolemia. Other vascular mechanisms, including cord ischemia due to shunt or steal phenomena, are unlikely since there was no abnormal cord MRI signal.

A similar case of cervical myelopathy after ventriculoperitoneal shunting was reported with MRI evidence of cord deformation associated with a shrunken subarachnoid space surrounded by dilated venous plexus.² However, that patient presented much earlier (15 months) after the shunt procedure and the nodular and diffuse pachymeningeal thickening and enhancement described in our case was not noted. Other reports suggest that the most com-

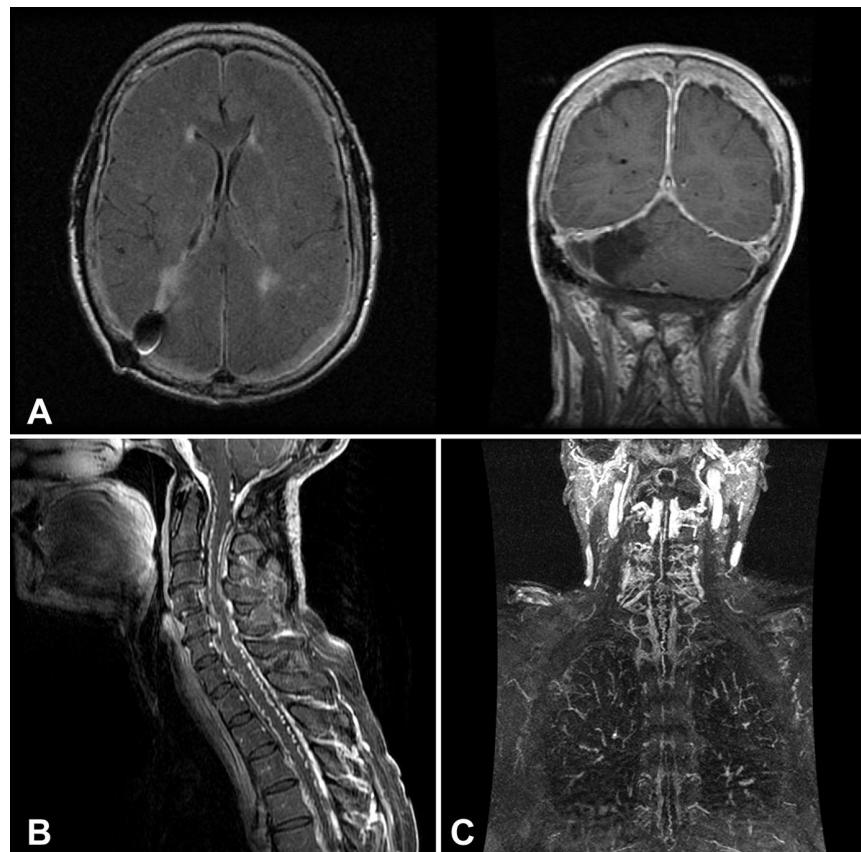


Figure. (A) Axial FLAIR image of the brain (left image) demonstrates a right parietal shunt and decompressed ventricles. Peripheral hyperintensity is due to dural thickening. Coronal gadolinium-enhanced T1-weighted brain MRI (right image) demonstrates diffuse dural thickening and enhancement and a postoperative defect in the right cerebellum. (B) Sagittal gadolinium-enhanced image of the cervical and upper thoracic spine demonstrates dural and epidural enhancement. The nodular enhancement ventral and dorsal to the cord is due to intradural vein prominence. (C) Coronal magnetic resonance angiography of the cervicothoracic spine demonstrates tortuous vessels. Evaluation for dural arteriovenous fistula was negative.

mon explanation for myelopathic symptoms in patients with CSF hypovolemia is cord compression from an extramedullary fluid collection; Lhermitte's symptom³ and radiculomyelopathy⁴ have been reported with such lesions in the setting of spontaneous or shunt-related CSF overdrainage. In most instances, spinal MRI features such as extradural or subdural fluid collections,^{5,7} meningeal gadolinium enhancement,^{5,6} and the presence of dilated epidural veins or venous plexus abnormalities^{6,7} are detected in patients with CSF hypovolemic symptoms for fewer than 6 months and no focal neurologic abnormalities.

The presence of cervical meningeal thickening with gadolinium enhancement or dilated epidural veins should alert one to the possibility of chronic CSF hypotension in a patient with myelopathy and a history of a CSF diversion procedure, even in the absence of postural headache and other characteristic symptoms of intracranial hypotension.

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PFO management: Neurologists vs cardiologists

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Patent foramen ovale (PFO) is associated with stroke, particularly in younger patients without another identifiable etiology. Therapeutic options available include antiplatelet medications, warfa-

rin, surgical closure, or percutaneous closure, yet there have been no adequate head-to-head trials to guide management decisions.¹ We conducted a survey of cardiologists and neurologists to determine current management strategies for patients with PFO.

Methods. In April 2004, a 17-item questionnaire (see the survey on the *Neurology* Web site at www.neurology.org) was sent to all neurologists and cardiologists participating as local principal investigators in the CLOSURE-I PFO closure trial (NMT medical), a study comparing PFO closure to medical management. The survey addressed practice patterns prior to participation in the trial focusing on PFO diagnosis, high risk characteristics, treatment choices, and alternative indications for PFO closure. Results were analyzed in aggregate and by specialty. Neurologists and cardiologists were compared using *t* tests or χ^2 tests as appropriate.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the July 12 issue to find the title link for this article.

Table Diagnostic and treatment strategies for patent foramen ovale (PFO) by specialty

	Neurologists, n = 47	Cardiologists, n = 46	p
Initial study to rule out cardioembolic source			
Transesophageal echocardiogram	34	37	
Transthoracic echocardiogram	62	63	0.25
Transcranial Doppler	4	0	
Distribution of treatments*			
Antiplatelet agents	49 ± 33	26 ± 26	0.0003
Warfarin	28 ± 26	17 ± 22	0.04
Surgical closure	2.3 ± 9	0.2 ± 0.8	0.05
Endovascular closure	20 ± 21	55 ± 34	0.0001
Have recommended PFO closure in an asymptomatic patient	2	9	0.2
Have recommended PFO closure for SCUBA diving	6	24	0.02
Have recommended PFO closure for migraines	0	14	0.01

Values are percentages. Responses are reported as mean ± standard deviation.

* Respondents reported the proportion of their patients that received each of the four options; the total was required to add up to 100%.

Results. A total of 108 neurologists and 129 cardiologists were surveyed. After two mailings, we received a response from 39% (44% of neurologists, 36% of cardiologists). Of respondents, 56% of cardiologists and 42% of neurologists were practicing in a community-based as opposed to academically based setting. All respondents (100%) felt that recurrent stroke risk was increased in the presence of an atrial septal aneurysm. A total of 62% felt that a larger shunt was associated with increased risk of recurrence while 47% felt that a larger distance between the septum primum and secundum was associated with increased risk. A total of 72% of respondents did not feel that age impacted future risk of stroke with PFO.

The table describes diagnostic and treatment strategies for PFO according to specialty.

Discussion. In 1877, Cohnheim first suggested that ischemic stroke may be caused by paradoxical embolism through a PFO.² Over a century later, case-control trials have confirmed an association between ischemic stroke and PFO, particularly in younger patients with cryptogenic stroke.^{3,4} However, there are no adequate comparative data available to guide treatment decisions.¹ Thus, given the confusing state of the literature, we undertook this survey to help define current management strategies for patients with PFO.

Overall, we found that surgical closure is rarely undertaken

while percutaneous closure is frequently recommended for stroke prevention. Across all physicians, we found a great deal of variability in the management of patients with PFO as noted by the large standard deviations for each therapeutic option. We also observed significant differences in the practice patterns of neurologists and cardiologists. In general, neurologists were more likely to favor conservative therapy such as antiplatelet medications, while cardiologists more often chose percutaneous closure for their patients. In addition, a sizable minority of physicians—predominantly cardiologists—have recommended percutaneous closure for asymptomatic patients, migraineurs, and SCUBA divers.

This survey included a balanced distribution of neurologists and cardiologists (the two specialties most likely to encounter these patients) and a mix of academic and nonacademic clinicians. Nevertheless, there are several limitations to this study. The practice patterns we report are influenced by the mix of patients that respondents see in their clinic. This survey did not investigate the types of patients that physicians encounter. Questionnaires were sent to neurologists and cardiologists who were already participating in a clinical trial addressing this topic. Therefore, respondents may not be representative of all practicing physicians as they have already demonstrated an interest in this subject. In addition, all cardiologists involved were interventionalists and were presumably actively performing endovascular closure. Thus, they may be more likely to recommend this procedure than the average cardiologist. Similarly, patients seen by cardiologists may have already been referred by a neurologist specifically for percutaneous closure. Finally, the response rate was only moderate, resulting in a potential response bias that may limit generalizability.

There are no published prospective randomized studies proving that closure is beneficial in preventing recurrent stroke.^{5,6} The Food and Drug Administration has issued a humanitarian device exemption (HDE) for the use of PFO closure devices in patients with stroke.⁷ However, the HDE restricts use of these devices to patients who have had recurrent strokes while on anticoagulation. This study suggests that many patients are receiving closure devices off label. There are currently three ongoing clinical trials in the United States comparing PFO closure to medical management for stroke prevention: The CLOSURE-I study (NMT medical), the RESPECT trial (AGA medical), and the CARDIA trial (CARDIA medical). Despite existing biases in clinical practice, the evidence for or against each treatment option is lacking, and whenever possible, physicians should encourage eligible patients to enroll in these studies.

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Bi-hemispheric anterior cerebral artery with drop attacks and limb shaking TIAs

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True drop attacks are characterized by a sudden fall without loss of consciousness. Cardiac disease and epilepsy are widely accepted causes, but other etiologies have been described, including vestibulopathy, hypothyroidism, third ventricle or posterior fossa cysts, cervical spine disease, and brainstem ischemia.¹⁻³ We present a case of drop attacks caused by an anomalous circle of Willis in the setting of a critical stenosis of the ipsilateral internal carotid artery (ICA).

Case report. A 73-year-old right-handed man with a history of hypertension and past smoking, on oral anticoagulation for atrial fibrillation, presented to an outside institution with several months of drop attacks. The episodes occurred one to four times per week and he described his legs giving out, seeing the floor "coming up," and then being on the ground. There were no prodromal symptoms such as lightheadedness, palpitations, or residual weakness after an attack. Witnesses confirmed no alteration in consciousness. He had a widened QRS by ECG and 24 hour ambulatory monitoring revealed about 10 2-second pauses. An EEG and brain MRI were normal and an MRA of the neck demonstrated stenosis of the ICA of 90%. A pacemaker was placed with a subjective decrease in frequency of the attacks, but without complete resolution. At this point the patient presented to our center.

Upon further questioning, he reported that in addition to the drop attacks he had shaking of the right arm, leg, or both, that would occur shortly after exertion. For example, he described shaking of the right arm lasting seconds, when reaching for a glass of water after coming in from mowing the lawn. His physical examination was notable for normal blood pressure in both arms, without orthostatic hypotension, and a left carotid bruit. The neurologic examination was normal. Doppler studies revealed a left ICA stenosis of 80 to 99%. Transcranial Doppler was used to measure cerebral vasodilatory capacity (CVC) as the percent rise in the ipsilateral middle cerebral artery mean flow velocity per 1 mm Hg PCO₂ after inhalation of 5% carbon dioxide in air. The CVC was impaired on the left (1.9%/mm Hg PCO₂) but normal on the right (6%/mm Hg PCO₂). A cerebral angiogram revealed a stenosis of the left ICA with the left A1 segment of the anterior cerebral artery (ACA) feeding both medial frontal lobes (figure, A and B). On right carotid injection there was no evidence of flow in the right A1 segment. Pial collaterals from the right middle and posterior cerebrals to the distal right ACA territory were seen (figure, C through E). The patient underwent carotid endarterectomy (CEA) resulting in complete resolution of his drop attacks and limb-shaking TIAs.

Discussion. Our patient was initially diagnosed with cardio- genic drop attacks and had a pacemaker placed. The partial improvement suggests a contribution of the atrial fibrillation or pauses in triggering the attacks. The left ICA stenosis seemed an unlikely cause of his bilateral leg weakness. However, both medial hemispheres were supplied from the left A1 segment of the ACA with agenesis or hypoplasia of the contralateral A1 segment, explaining the sudden falls. Agenesis has been documented in up to 2%, and hypoplasia in up to 10%, of cases.⁴ Limb-shaking TIAs provided an essential clue in this case and are increasingly recognized as due to perfusion failure, often from ICA stenosis. Focal stenosis of the distal A2 segment of the ACA has also been reported.^{5,6} Decreased cerebral vasodilatory capacity in response to inhalation of 5% carbon dioxide has been associated with a higher risk of later ischemic events.⁷ Evaluation of hypoperfusion due to focal stenosis should be considered in patients presenting with unexplained drop attacks. A history of limb shaking TIAs may suggest the underlying cause.

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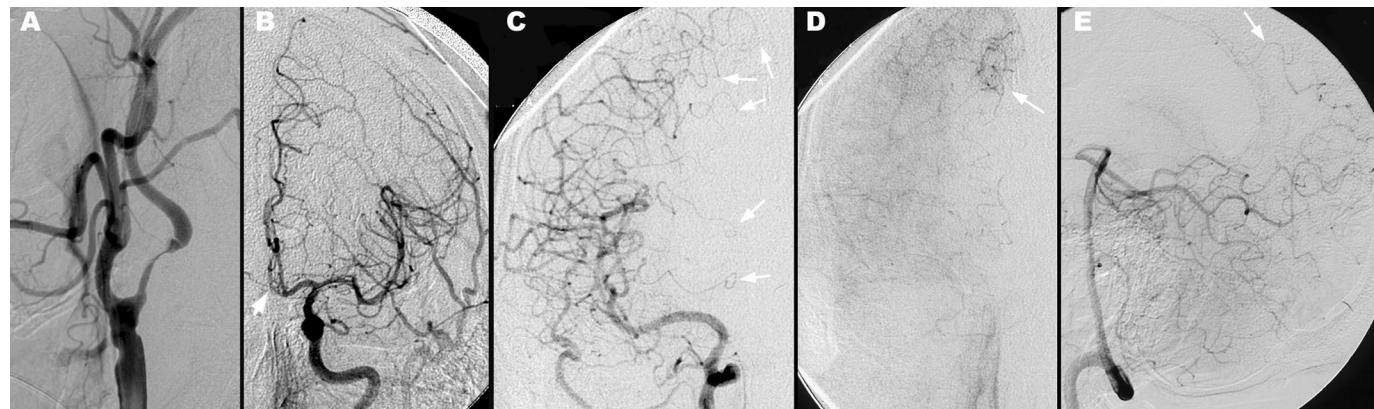


Figure. Angiogram: (A) Left carotid frontal view showing critical stenosis at the bifurcation. (B) Left carotid injection frontal view with the left anterior cerebral (ACA) A-1 segment supplying the right A-2 branch (arrow). (C) Right carotid injection frontal view showing no filling of the right ACA A-1 segment and early pial collaterals to the ACA territory (arrow). (D) Later phase than C showing pial collaterals from the right middle cerebral to the ACA territory (arrows). (E) Left vertebral injection lateral view showing pial collaterals from the right posterior cerebral to the ACA territory (arrow).

Serial diffusion and perfusion-weighted MR in transient hypoglycemia

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Hypoglycemia may mimic acute stroke. We report a patient with a stroke-like episode and corresponding transient unilateral MR changes due to hypoglycemia.

Case report. A 24-year-old woman was admitted for left hemiparesis of sudden onset. She had no vascular risk factors. Three months before admission, she experienced two episodes of generalized seizures in the context of sleep deprivation. EEGs were normal. Two months later, she had two episodes of transient right hemiparesis. She never experienced headaches during or after these episodes. Head CT scan, cervical Doppler, and transthoracic echocardiography were normal. Routine blood tests, autoimmune screening, and lumbar puncture were normal.

She was admitted for a pure left motor deficit of sudden onset. Two hours after onset, the NIHSS score was 3. FLAIR was normal, while a right internal capsule hypersignal was seen on DWI with decreased ADC values (figure 1). First-pass gadolinium perfusion sequence (PWI) showed a slight increase of relative cerebral blood volume (20% compared to contralateral hemisphere) restricted to the lesion seen on DWI, without arterial occlusion on intracranial three-dimensional time of flight MR angiography. EKG, body temperature,

and blood pressure were normal. A second MRI, performed 4 hours after onset because of neurologic worsening (NIHSS score at 7), showed a clear-cut hypersignal in the right internal capsule on routine DWI, with unchanged PWI finding. Routine blood tests were normal except for a glucose level of 2.2 mmol/L (normal > 3.5 mmol/L). The deficit completely resolved in 6 hours and DWI-PWI MRI obtained 12 hours after onset returned to normal (figure 1). Cervical MR angiography, EKG monitoring, and transesophageal echocardiography were normal. An endocrine evaluation was suggestive of insulinoma. A pancreatic tumor was found and successfully operated a few days later. Six months after surgery, the patient has remained asymptomatic.

Discussion. MRI reports of hypoglycemic-induced lesions are limited,¹⁻³ and mainly concern patients with profound hypoglycemic coma.^{3,4} Lesions typically involve cerebral cortex, hippocampus, basal ganglia, and also middle cerebellar peduncles,^{3,5} bilaterally. It has been suggested that DWI changes in hypoglycemic coma portend a poor outcome. There is no consensus regarding the vulnerability of cerebral regions to hypoglycemia. Glucose deprivation leads to severe brain energy failure and a reduction of cell membrane ionic pump activity. In experimental hypoglycemia, lesions involve the cortex, hippocampus, and usually respect the white-matter and the cerebellum while significant ADC reduction in the overall brain has been reported.⁶

We report a unilateral and transient DWI increased signal with decreased ADC in a patient with a stroke-like episode due to an insulinoma. Initially, DWI and ADC were more sensitive than FLAIR images, which were normal 2 hours after onset. The ADC values were moderately decreased and similar to ADC values reported in TIA. Despite initial ADC decrease, the lesion was fully reversible, similar to a recent case report.² We also noted a hyperperfusion within the DWI lesion. Even if caution is needed given the small size of the lesion, experimental and clinical observations indicate that insulin-induced hypoglycemia produces cerebral vasodilation, presumably resulting from dysfunction of the oxide pathway.⁷

Thus hypoglycemia not only mimics TIA clinically but radiologically.

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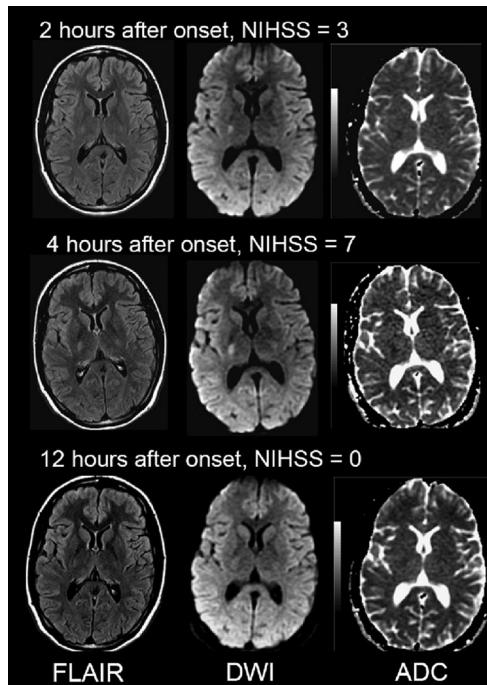


Figure. Transient signal changes on serial MRI in hypoglycemia. Two hours after onset, the FLAIR image was normal while DWI showed a unilateral hypersignal in the right internal capsule with decreased ADC values (20% decreased). Four hours after onset, a slight signal increase was seen on FLAIR images with a clear-cut signal increase on DWI. Twelve hours after onset, the clinical symptoms had resolved and the MRI returned to normal.

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