Should thrombolysis be given to a stroke patient refusing therapy due to profound anosognosia?

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A 70-year-old woman was told by a neighbor that her speech was slurred. She was also having difficulty standing. She was brought to the emergency room within 45 minutes of symptom onset stating "they said I had a stroke, but I didn't." She had a history of hypertension, hypercholesterolemia, and stage IV non-small cell lung cancer. Her examination was notable for a severe anosognosia, dysarthria, a right gaze preference, and left homonymous hemianopia, hemiparesis, hemihypesthesia, and visual, tactile, and spatial neglect. Her NIH Stroke Scale score was 15. Head CT was unremarkable, and she had no contraindications for IV thrombolysis.

Preparations were made for the administration of tPA, at approximately 2 hours after symptom onset. The patient, however, vehemently refused therapy because she did not believe she was having a stroke. Attempts were made to contact the patient's family, but this did not prove possible until after the 3-hour time window had elapsed. Upon discharge to our acute rehabilitation facility, the patient required maximal assist for transfers, remained hemiparetic, and had persistent neglect and hemianopia.

Although the administration of tPA does not require written informed consent, the risks and benefits of this therapy must be explained to the patient and family to the greatest extent possible.[1] According to the American Academy of Neurology (AAN) position paper,[2] tPA may be given without consent, if considered an accepted standard of care, in keeping with the doctrine of emergency treatment and implied consent. This would apply in particular to patients who are unable to speak due to acute aphasia. Our patient differs in that she was interactive and talkative, and was actively refusing to be treated. Because her anosognosia prevented her from properly comprehending the nature of her medical situation, she was only partially competent to make this decision.[3] Her lack of complete competency, however, still may not warrant treating her against her will. tPA has long-term benefits but also carries a trade-off of short term risk (including potentially fatal intracerebral hemorrhage). Under the pressure of a tense emergency situation, some patients may not be willing to accept this risk even without anosognosia complicating the discussion.

Since up to half of all stroke cases might involve a portion of the right middle cerebral artery and produce a component of anosognosia, we would hypothesize that our case is not entirely unusual. In an effort to expand the number of patients eligible for tPA, while ensuring compliance with valid informed consent, we would propose that the AAN consider updating its guidelines to incorporate anosognosia.

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References

1. Fleck LM, Hayes OW. Ethics and consent to treat issues in acute stroke therapy. Emerg Med Clin North Am 2002;20:703–715.
2. American Academy of Neurology. Consent issues in the management of cerebrovascular diseases. A position paper of the American Academy of Neurology Ethics and Humanities Subcommittee. Neurology 1999;53:9–11.
3. Ethical practice. In: Bernat JL. Ethical issues in neurology, 2nd ed. Butterworth-Heinemann, 2002;27–49.

CSF hypocretin-1 (orexin-A) levels in childhood narcolepsy and neurologic disorders

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Hypersomnia and cataplexy expression in childhood narcolepsy are often different from adult cases, making diagnosis difficult.[1] The Multiple Sleep Latency Test (MSLT) for demonstrating hypersomnia and sleep-onset REM periods has not been standardized for children under age 8[2] and has limited value in pediatrics.

CSF hypocretin-1 measurements were established as a new diagnostic tool for narcolepsy–cataplexy in adults[3-5] but has not yet been evaluated in children.[4] We measured CSF hypocretin-1 levels in 132 children with various neurologic disorders (including six narcoleptic children) to evaluate the diagnostic value of CSF hypocretin measures for childhood narcolepsy.

Patients and methods. We analyzed previously collected data, gathered from 1992 to 2003 for diagnostic and research purposes, including CSF samples (n = 132, including 14 cases previously reported), collected from patients (under age 20 from seven Japanese hospitals) with neurologic disorders (the core experimental protocol was approved at Akita University in August 2002; the local ethical committee approved the use of CSF samples). Patients were categorized based on the diagnosis determined by individual clinical records (table). Patients without complete records or definite diagnosis were excluded. Narcolepsy was diagnosed by the criteria of the International Classification of Sleep Disorders.[6]

Hypocretin-1 was measured by direct radioimmunoassay of CSF stored at −80 °C (detection limit 40 pg/mL).[7] As there was no difference in the mean CSF hypocretin level between children and adults,[7] the levels were defined as low (<110 pg/mL), intermediate (≥110 to ≤200 pg/mL), and normal (>200 pg/mL).[5] The low value represents 30% of the mean value of normal adult CSF hypocretin and has the best sensitivity/specificity ratio for diagnosing adult narcolepsy.[5]

Results. Low CSF hypocretin-1 levels were observed in all six narcoleptic subjects (mean age 9.7 years; 6 to 16 years) (see the table; see also table E-1 on the *Neurology* Web site at www.neurology.org). All narcoleptic subjects had positive human leukocyte antigen DR2 markers. The duration of hypersomnia (DH) was 1 to 20 months prior to the CSF sampling. In two of these patients (DH: 1 and 2 months), the clinical diagnosis of narcolepsy was not clear at the time of the CSF sampling. Nevertheless, they later exhibited cataplexy, a typical symptom of narcolepsy.

In four neurologic categories, Guillain–Barré syndrome (GBS) (6/6), acute disseminated encephalomyelitis (ADEM) (2/7), brain tumor (2/4), and head trauma (3/3), 13 children had low to intermediate hypocretin-1 levels (see the table; also see table E-2 on the *Neurology* Web site).

All GBS subjects in this study showed reduced CSF hypocretin levels. Only one case (151 pg/mL) exhibited short sleep latency (<1 minute) by a two-nap test after the recovery of the neurologic symptoms. Two ADEM cases (102 and 146 pg/mL) presented transient sleepiness associated with bilateral hypothalamic lesions on MRI. Two subjects with head trauma and two with brain tumor reported sleepiness, and these subjects together with one subject with head trauma without sleepiness had reduced levels.

Intermediate hypocretin-1 levels were also found in some neuropediatric-specific conditions, such as Prader–Willi syndrome

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Table *CSF hypocretin-1 levels in various neurologic disorders*

Diagnosis	n	Low, <110 pg/mL	Intermediate, 110–200 pg/mL	Mean hypocretin-1 level (range), pg/mL
Narcolepsy (EDS with/without cataplexy, all are DR2 positive)	6	6	0	(L–79)
MSL ≦8 min + ≧2 SOREMPs	4	4	0	<40
MSL ≦8 min + no SOREMPs	2	2	0	<40, 79
Other primary hypersomnia (recurrent hypersomnia, idiopathic hypersomnia)	5	0	0	263 (232–292)
CNS infection (meningitis, encephalitis, cerebellitis)	22	0	2	282 (156–423)
Autoimmune and postinfectious disease	18	3	5	202 (L–366)
GBS	6	2	4	
ADEM	7	1	1	
Others (MS, CIDP, myelopathy)	5	0	0	
Head trauma (subdural hematoma, diffuse axonal injury, contusion)	3	1	2	132 (56–192)
Brain tumor (hypothalamic tumor, thalamic tumor)	4	1	1	175 (102–257)
Malignancy without CNS invasion (leukemia, lymphoma)	12	0	0	297 (232–364)
Psychological/psychiatric status (depression, hysteria)	3	0	0	303 (265–345)
CNS malformations (migration disorder, brain anomaly)	8	0	0	270 (223–383)
Chromosome aberration (PWS, tuberous sclerosis, Sturge–Weber syndrome)	5	0	1	233 (192–310)
Epilepsy or mental retardation of unknown origin (epilepsy, mental retardation, infantile spasms)	19	0	2	286 (124–372)
Perinatal asphyxia and trauma (cerebral palsy)	2	0	0	307 (304–310)
Metabolic or degenerative diseases (NPC, mitochondria encephalopathy, leukoencephalopathy, spinocerebellar degeneration)	6	0	1	307 (142–461)
Chronic CNS infection (SSPE)	2	0* (2)	0	313 (311–315)
Epileptic encephalopathy (progressive myoclonic encephalopathy, Lafora disease, Rasmussen encephalopathy)	3	0	0	290 (215–348)
Motor unit disease (congenital myotonic dystrophy, spinal muscular atrophy, congenital myopathy)	4	0	0	307 (265–338)
Cerebral hypertension (idiopathic cerebral hypertension, hydrocephalus)	2	0	0	320 (280–360)
Transient neurologic conditions (suspected meningitis but negative culture, migraine)	8	0	1	279 (195–338)
Total	132	11* (13)	15	

When patients received multiple CSF taps, the values during the most representative phase of the disease are reported.

* Undetectably low levels under interferon-α treatment.

L = low levels; EDS = excessive daytime sleepiness; MSL = mean sleep latency; SOREMPs = sleep-onset REM periods; GBS = Guillain–Barré syndrome; ADEM = acute disseminated encephalomyelitis; MS = multiple sclerosis; CIDP = chronic inflammatory demyelinating polyneuropathy; PWS = Prader–Willi syndrome; NPC = Niemann–Pick type C; SSPE = subacute sclerosing panencephalitis.

(PWS) (1/1), infantile spasms due to birth trauma of unknown origin (2/3), Niemann–Pick type C (NPC) (1/2), CNS infection (2/22), and febrile convulsion (1/3). None of these patients showed hypersomnia, but the NPC case with intermediate hypocretin level (147 pg/mL) presented cataplectic-like episodes.

Discussion. Five subjects in four diagnostic categories (GBS, ADEM, brain tumor, and head trauma) showed low hypocretin levels. Partial impairments of hypocretin systems secondary to hypothalamic damage may be responsible for decreased hypocretin levels (and some rare hypersomnia cases). Clinical symptoms and other diagnostic findings (such as MRI) are useful in differentiating these cases from narcolepsy, so low hypocretin levels in these diseases do not confound the diagnostic value for narcolepsy.

High percentages of low levels of GBS and ADEM are interesting because they may suggest immune-mediated damage of hypocretin neurons. A similar mechanism may also be involved in hypocretin-deficient idiopathic narcolepsy. Intermediate levels were seen in a neonatal case of PWS prior to the appearance of hypersomnia and obesity. PWS may thus be a model for congenital dysfunction/developmental failure of the hypocretin system. Similarly, the NPC case with cataplectic-like episodes may be a model for acquired deterioration of the hypocretin system by accumulation of lipids in the brain structures responsible for the induction of cataplexy.

There may be some false negatives in the presumed nonnarcoleptic group, as this group did not receive the same series of

evaluations as the narcolepsy group, including polysomnography and MSLT. Nevertheless, with any of the other neurologic disorders, a concomitant diagnosis of narcolepsy is relatively improbable based on their overall clinical presentations. Low CSF hypocretin levels were consistently found in all narcoleptic subjects. In addition, these levels were occasionally found prior to classic narcoleptic signs and symptoms. There may be a true, relatively independent diagnostic utility in measuring CSF hypocretin levels when narcolepsy is suspected in children.

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References

1. Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. Ann Neurol 1998;43:135–142.
2. Palm L, Persson E, Elmqvist D, Blennow G. Sleep and wakefulness in normal preadolescent children. Sleep 1989;12:299–308.
3. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000;355:39–40.
4. Ripley B, Overeem S, Fujiki N, et al. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. Neurology 2001;57:2253–2258.
5. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553–1562.
6. American Academy of Sleep Medicine. International Classification of Sleep Disorders, rev.: diagnostic and coding manual. Rochester, MN: American Academy of Sleep Medicine, 2001.
7. Kanbayashi T, Yano T, Ishiguro H, et al. Hypocretin-1 (orexin-A) levels in human lumbar CSF in different age groups: infants to elderly persons. Sleep 2002;25:337–339.

Aortic dissection presenting with transient global amnesia-like symptoms

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Diagnostic criteria of transient global amnesia (TGA) are witnessed attacks, clear-cut anterograde amnesia during the attack, absent clouding of consciousness and loss of personal identity, no accompanying focal neurologic symptoms or epileptic features, resolution of attacks within 24 hours, and no recent head injury or active epilepsy.[1] For the etiology of TGA, four main hypotheses have been considered: TIA, epilepsy, migraine, and transient venous ischemia.[1-3] None of these hypotheses fully explains the mechanism of this episodic disease, but the accepted neuroanatomic correlate of TGA is the mediobasal temporal lobe and hippocampus. We present two patients with aortic dissection who provide evidence for an ischemic pathogenesis in TGA.

Case reports. Patient 1. A 47-year-old man was found confused and disoriented. On examination at admission, he asked repetitive questions and was alert but completely disoriented to time and place and only partially oriented to person. The cranial nerve examination showed only a slight anisocoria. The pronator drift test revealed a discrete motor deficit of the left side, accompanied by a mildly increased reflex activity. The cranial CT was unremarkable. The EEG revealed no epileptic discharges. Some hours later, the patient was reoriented with an amnestic gap for the attack's duration, and the neurologic deficit had completely resolved. Because of persistent hypotension, a chest radiograph was taken, which revealed a widening of the mediastinum. A CT scan of the chest and abdomen revealed a dissecting aneurysm (Stanford type A) of the aortic arch starting at the aortic valve, involving both carotid arteries and the left subclavian artery, and continuing into both iliac arteries (figure).

Patient 2. A 61-year-old woman was taken to hospital because of acute chest pain. On admission, she had retrograde amnesia for the past few hours, anterograde amnesia with inability to learn new facts, and repetitious questioning. Neurologic examination revealed a mild right facial paresis. Cranial CT was unremarkable. Five hours after onset of symptoms, she was reoriented with an amnestic gap. Because of the initial thoracal pain and our knowledge of the first reported patient, an aortic dissection was considered. Chest radiograph was normal, but a CT scan of the chest and abdomen revealed a dissection of the aorta (Stanford type A) starting at the aortic valve, involving all supra-aortal branches, and ending above the left renal artery.

Discussion. Patients with TGA can be distinguished into three groups: "pure TGA" patients who fulfill all diagnostic criteria; patients with probable epileptic amnesia; and patients with probable transient ischemic amnesia. The third group includes patients with additional neurologic deficits during the attack as in our patients.[1] Although we found no proof of ischemic lesions in the cranial CT in our patients, the minor neurologic deficits suggested cerebral ischemia. MRI including diffusion-weighted MRI (DWI) would have been helpful to characterize the etiology, but both patients underwent immediate surgery without possibility for further diagnostics. We presume that an aortic dissection can cause a TGA subtype with ischemic etiology, which can be called transient ischemic amnesia. The underlying mechanism may be an embolic vascular occlusion in the posterior circulation, thus causing an embolic TIA with an unusual TGA-like TIA syndrome. The ischemic hypothesis in TGA was enforced by bitemporal hypoperfusion found in brain SPECT.[4] However, patients with TGA have fewer thromboembolic risk factors and smaller risk of cerebral infarction compared with those with TIA.[1] The DWI findings provide conflicting results concerning a possible ischemic mechanism.[5] In one study using DWI in 10 patients with TGA, 7 patients showed an elevated signal intensity in the left or in both temporomesial regions. This was interpreted as a hint of the possible etiologic role of spreading depression.[6] One-third of patients with TGA also have migraine. The low recurrence rate of ~8% in TGA and the different age distribution are arguments against migraine as a pathogenic mechanism.[1] The weakest evidence is

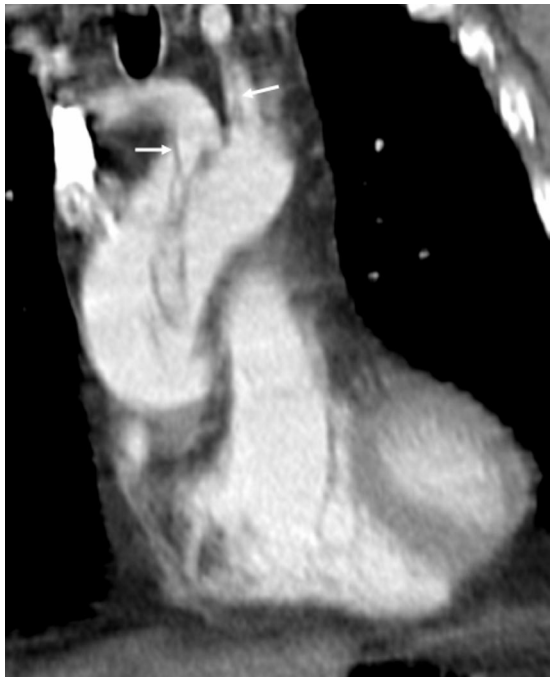

Figure. Multiplanar reconstructions from spiral CT: multiple dissection membranes within the aortic arch are demonstrated with involvement of the supra-aortic branches (arrows).

found for an epileptic genesis because of the longer duration of TGA attacks and the absence of epileptic changes. Some authors favor a mechanism of retrograde venous congestion from the superior vena cava to cerebral veins.[2] Both of our patients had no history of migraine, epilepsy, or stroke but did have hypertension for several years.

As shown, aortic dissection is a possible cause of TGA. For any patient who does not fulfill the criteria of pure TGA, it is necessary to exclude other probable causes such as aortic dissection, especially if there is any history of chest pain, unexplained hypotension, or pathologic findings on chest radiographs.[7]

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References

1. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. J Neurol Neurosurg Psychiatry 1990; 53:834–843.
2. Lewis SL. Aetiology of transient global amnesia. Lancet 1998;352:397–399.
3. Tong DC, Grossman M. What causes transient global amnesia? New insights from DWI. Neurology 2004;62:2154–2155.
4. Stillhard G, Landis T, Schiess R, Regard M, Sialer G. Bitemporal hypoperfusion in transient global amnesia: 99m-Tc-HM-PAO SPECT and neuropsychological findings during and after an attack. J Neurol Neurosurg Psychiatry 1990;53:339–342.
5. Huber R, Aschoff AJ, Ludolph AC, Riepe MW. Transient global amnesia. Evidence against vascular ischemic etiology from diffusion weighted imaging. J Neurol 2002;249:1520–1524.
6. Strupp M, Brüning R, Wu RH, Deimling M, Reiser M, Brandt T. Diffusion-weighted MRI in transient global amnesia: elevated signal intensity in the left mesial temporal lobe in 7 of 10 patients. Ann Neurol 1998;43:164–170.
7. von Kodolitsch Y, Nienaber CA, Dieckmann C, et al. Chest radiography for the diagnosis of acute aortic syndrome. Am J Med 2004;116:73–77.

Bilateral carotid artery dissection with thyrotoxicosis

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Spontaneous internal carotid artery dissection (ICAD) is a major cause of stroke in young adults.[1] Environmental factors, such as minor trauma and mechanical stretching, may trigger the dissection, especially in patients with an underlying arteriopathy. Despite the direct vascular effects of thyroid hormones (THs),[2-4] the predisposition for arterial dissection has not been identified in Graves disease (GD). We describe two women with bilateral ICAD and GD with fatal outcome, one with histopathologic study.

Case reports. Patient 1. A 45-year-old woman with irregular treatment for GD was admitted after 6 hours of right hemiparesis and aphasia. She had no vascular risk factors. On admission, her blood pressure was 130/80 mm Hg, and her pulse was 150 beats/min. She presented a mild nonfluent aphasia and right-sided hemiparesis. EKG showed sinusal tachycardia. Brain CT showed an ischemic infarct in left middle cerebral artery (MCA) territory. Angiography detected bilateral irregular high-grade stenosis starting ~2 cm distal to the carotid bulbs and extending to the base of the skull, suggesting ICAD. Anticoagulation was started. After 24 hours, the patient deteriorated with left-sided hemiparesis and right hemianopia. MRI showed infarctions in the territory of the right anterior cerebral artery and both MCAs. One month later, she deteriorated with decerebrate rigidity and died. Brain CT revealed diffuse edema and midline shift.

Patient 2. A 33-year-old woman with poorly controlled GD was admitted after 3 days of left hemiparesis and aphasia. She had no vascular risk factors. She was febrile; her blood pressure was 180/110 mm Hg, and her pulse was 146 beats/min. She had left-sided hemiplegia, right-sided hemiparesis, global hyperreflexia, left Babinski sign, right conjugated gaze palsy, and drowsiness. EKG showed sinusal tachycardia. Brain CT revealed infarctions in both MCA territories. Angiography showed bilateral high-grade stenosis starting ~3 cm distal to the carotid bulbs and extending to the base of the skull, suggesting ICAD. Anticoagulation was started. She deteriorated during the next 24 hours with decerebrate rigidity. Brain CT showed marked infarctions in both internal carotid artery territories, edema, and midline shift. She died 2 days later.

Postmortem examination macroscopic findings were diffuse and small hemorrhagic lesions at pons, severe infarctions in both MCA territories, and edema with bilateral uncal and tonsillar herniation. The circle of Willis and its major branches were unremarkable. Both internal carotid arteries presented multifocal media degeneration with intracellular and extracellular vacuoles, sometimes coalescing to form cysts, and areas of marked wall thinning. There were also deposits of Alcian blue/periodic acid–Schiff-positive substances in the degenerating media. The intima was focally thickened, and the internal elastic lamina was absent in some areas and reduplicated and distorted in others (figure).

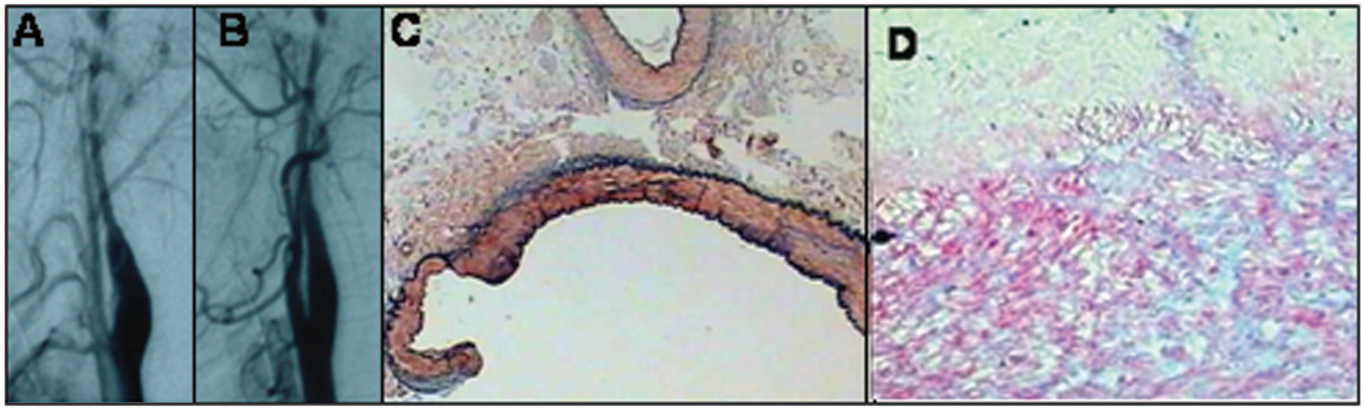

Figure. Angiography showing right (A) and left (B) internal carotid artery dissection. (C) Cross-section of the right internal carotid artery. There is focal tunica media thinning and an area of duplication and distortion of the internal elastica lamina on the left edge of the artery (Elastica–Verhoff stain, ×25). (D) Cross-section of the left internal carotid artery. Tunica media showing vacuolar degeneration with intracellular and extracellular vacuoles and deposits of Alcian blue/periodic acid–Schiff-positive substances (×400).

Similar alterations were also observed in the aorta and external carotid and celiac arteries. These findings were consistent with segmental mediolytic arteriopathy (SMA).

Discussion. Cerebrovascular morbimortality in patients with GD is often related to heart changes, such as arrhythmias and cardioembolism.[2] However, THs can also affect the vascular system through direct effects on smooth muscle cells and endothelium, accounting for marked basal vasodilation, abnormal vascular reactivity, and changes in endothelial vasoactive factor secretion.[2-4] Despite these vascular effects, the predisposition for arterial dissection has not been reported in GD, perhaps because patients with arterial dissection are not routinely investigated for thyroid diseases. Although the association between GD and arterial dissection may be a coincidence in our patients, considering the direct vascular effects of THs, we hypothesize that in susceptible individuals, THs could modify the arterial microstructure, interfere with their mechanical properties, and predispose to dissection.

Postmortem examination in one patient revealed SMA, a rare noninflammatory arterial disease characterized by a lytic process of the media, which can facilitate dissection. Its etiology is uncertain but may be related to autoimmune disorders.[5] Specific serologic studies for other autoimmune disorders were not performed in our patients. Although there is a reported case of SMA in a patient with systemic lupus erythematosus,[5] but not in GD, it is not possible to rule out an immune-mediated mechanism between SMA and GD.

GD, through its hemodynamic or direct vascular effects, or even by means of an immune-mediated vascular mechanism, may predispose ICAD in patients with an underlying arteriopathy.

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References

1. Schievink WI. Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med 2001;344:898–906.
2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001;344:501–509.
3. Napoli R, Biondi B, Guardasole V, et al. Impact of hyperthyroidism and its correction on vascular reactivity in humans. Circulation 2001;104:3076–3080.
4. Donnini D, Ambesi-Impiobato FS, Curcio F. Thyrotropin stimulates production of procoagulant and vasodilative factors in human aortic endothelial cells. Thyroid 2003;13:517–521.
5. Junoven T, Niemelä O, Reinilä A, Nissinen J, Kairaluoma MI. Spontaneous intraabdominal haemorrhage caused by segmental mediolytic arteritis in a patient with systemic lupus erythematosus—an underestimated entity of autoimmune origin? Eur J Vasc Surg 1994;8:96–100.

Intra-arterial thrombolysis of complete deep cerebral venous thrombosis

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Cerebral venous thrombosis (CVT) is one cause of stroke presenting with variable symptoms, mainly caused by individual variations in the cerebral venous drainage. Involvement of the deep venous system is associated with a poor prognosis.[1] Despite anticoagulant treatment,[2] some patients continue to deteriorate. In such cases, the local administration of thrombolytic agents into the cerebral venous system has been reported.[3]

We report a patient with extensive deep CVT who was treated with intra-arterial infusion of recombinant tissue plasminogen activator (rt-PA) into both internal carotid arteries and the left vertebral artery. A complete resolution of the thrombus resulted, and clinical recovery was excellent.

Case report. A 49-year-old man was treated with oral anticoagulation for a hereditary antithrombin (AT-III) deficiency, which had previously led to a thrombosis of the superior sagittal sinus at age 30 years and a pulmonary embolism at age 43 years. Anticoagulation was discontinued 4 weeks before symptom onset because of scheduled dental work. The day before admission the patient had headache and decreasing level of consciousness. On admission, he was stuporous, had slurred speech, severe hemiparesis, and multimodal hemineglect on the left side. The level of D-dimer was increased to 30.3 μg/mL, and AT-III activity was reduced to 41%. Results of other blood tests were normal. Cranial CT and MRI showed bilateral right pronounced edema in the thalamic nuclei extending into the midbrain (figure, C and E). MR angiography revealed fresh thromboses of the inner veins. The patient was treated with heparin IV to increase partial thromboplastin time to 2.5 to 3 times the normal range. Nevertheless, the patient continued to deteriorate. Therefore, the decision was made to attempt an endovascular recanalization. The cerebral angiogram confirmed complete occlusion of the deep venous system (figure, A). Because stagnation of the different inner veins was present from three different arterial vascular territories, one 5-French Envoy (Cordis, Miami Lakes, FL) catheter was placed into each internal carotid artery, and one 5-French Envoy catheter was placed into the left vertebral artery (T.E.M.). Thrombolysis was performed with 5 mg rt-PA through each catheter, resulting in a dose of 15 mg rt-PA/h. After 3 hours and administration of 45 mg rt-PA, the inner venous system was completely recanalized (figure, B).

A CT scan immediately after treatment gave no evidence of intracranial hemorrhage. An MRI scan 5 days after thrombolysis showed resolution of the edema on the left and a decrease on the right (figure, D and F). The patient was later treated with IV heparin and oral anticoagulation. He improved dramatically, and his only symptom on discharge was a discrete disturbance of the left-sided fine motor activity.

Discussion. Deep venous thrombosis is associated with a grave prognosis.[1] Despite anticoagulation and symptomatic therapy, some patients continue to deteriorate. Because this was the situation in our patient, a more invasive therapy with intra-arterial thrombolysis was initiated. Although there are no evidence-based data on thrombolysis in CVT, local thrombolysis via the venous system has been attempted, as has systemic thrombolysis, but there are no data about intra-arterial thrombolysis in CVT, except for one case report that combined rheolytic thrombectomy (AngioJet, Possis Medical, Inc., Minneapolis, MN) with intra-arterial thrombolysis.[4]

The advantage of intra-arterial compared with local venous thrombolysis in our case was the rapid effect (3 hours). This was perhaps a result of the higher concentrations of thrombolytics in the inner cerebral veins, which were transported via the physiologic blood flow. This hypothesis is supported by an analysis of the duration of thrombolysis in previous studies, which showed that thrombolysis via the venous system was much more time consuming (41 ± 49 hours).[3]

An alternative strategy in the case of extensive thrombosis of the sinuses may be mechanical recanalization.[5] This was not required in our patient; however, in the case of extensive dural sinus involvement, the combination of transarterial fibrinolysis of the veins and mechanical recanalization of the sinuses seems to be reasonable.

Despite its advantages, our approach may have limitations. Intra-arterial infusion of thrombolytic agents may increase the risk of additional hemorrhages in the infarcted area because the agents have to pass the microvessels in the damaged region, which may be severely affected by CVT.[6] However, one study showed recanalization of the dural sinuses by rheolytic thrombectomy and accomplished the recanalization of the superficial cerebral veins by transarterial fibrinolysis despite the presence of intracranial hemorrhages in two cases.[4] We used catheters in three vascular territories for low-dose fibrinolysis (5 mg/h each). The reason was to reach all affected inner veins.

Intra-arterial thrombolysis for deep CVT may be a promising new treatment modality. Unquestionably, larger studies are required to determine the value and best technique of intra-arterial fibrinolysis in CVT.

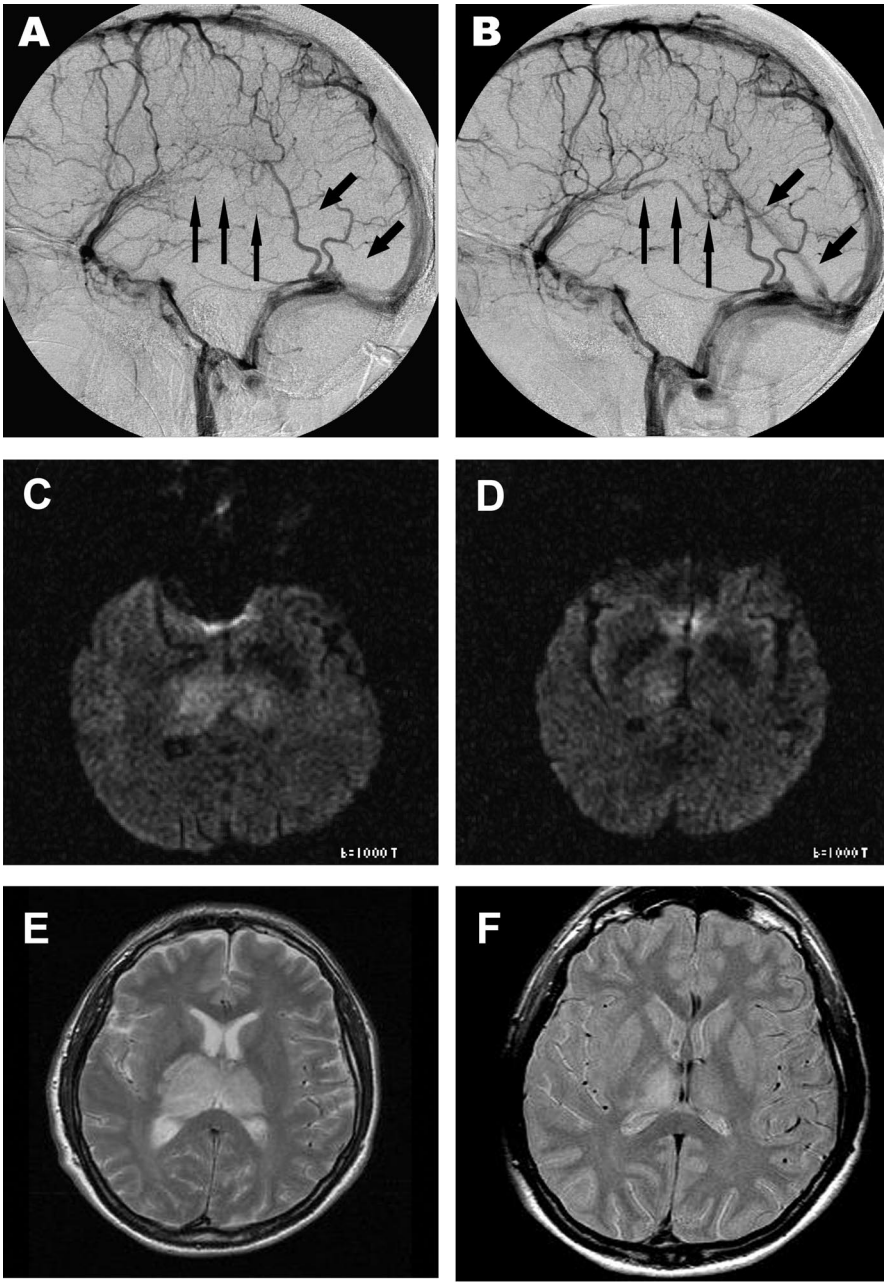

Figure. (A) Right internal carotid angiogram (late venous phase, lateral view) before treatment. None of the inner cerebral veins or the straight or inferior sagittal sinus is visualized (arrows on straight sinus and right internal cerebral vein). (B) Right internal carotid angiogram (late venous phase, lateral view) performed after intra-arterial thrombolysis. The internal cerebral veins, vein of Galen, and the straight sinus are recanalized (the hypoplastic inferior sagittal sinus was only filled by the left internal carotid and the basal veins of Rosenthal through the vertebrobasilar system, not shown). (C) Axial diffusion-weighted MRI after admission of the patient to the hospital showed extensive bilateral thalamic edema. (D) Diffusion-weighted MRI 5 days after treatment with recombinant tissue plasminogen activator showed resolution on the left and a marked decrease of the lesion in the right thalamus. (E) T2-weighted MRIs showed increased signal and marked swelling of the right more than of the left thalamus, including the right inner capsule. (F) T2-weighted MRI after treatment revealed a complete release of the space-occupying effect, normalization of the signal on the left, and remnant increased signal on the right with flow void of the inner veins.

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References

1. Haley EC Jr, Brashear HR, Barth JT, Cail WS, Kassell NF. Deep cerebral venous thrombosis. Clinical, neuroradiological, and neuropsychological correlates. Arch Neurol 1989;46:337–340.
2. Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. Lancet 1991;338:597–600.
3. Canhao P, Falcao F, Ferro JM. Thrombolytics for cerebral sinus thrombosis: a systematic review. Cerebrovasc Dis 2003;15:159–166.
4. Chow K, Gobin YP, Saver J, et al. Endovascular treatment of dural sinus thrombosis with rheolytic thrombectomy and intra-arterial thrombolysis. Stroke 2000;31:1420–1425.
5. Soleau SW, Schmidt R, Stevens S, Osborn A, MacDonald JD. Extensive experience with dural sinus thrombosis. Neurosurgery 2003;52:534–544.
6. Vosko MR, Rother J, Friedl B, et al. Microvascular damage following experimental sinus-vein thrombosis in rats. Acta Neuropathol (Berl) 2003;106:501–505.

Severe hemiplegic migraine attack precipitated by fentanyl sedation for esophagogastroscopy

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Hemiplegic migraine is a very rare subtype of migraine. Familial hemiplegic migraine is an autosomal dominant trait, and mutations in three different genes encoding structural proteins of voltage-gated P/Q calcium channel and the membrane sodium–potassium ATPase pump[1] have been implicated in its pathogenesis. Sporadic hemiplegic migraine may reflect spontaneous mutations or incomplete penetrance.

We report a case of a severe and prolonged hemiplegic migraine attack precipitated by sedation for an endoscopic procedure in a patient with sporadic hemiplegic migraine. We reviewed the medical literature and discuss two other similar case reports.

Case reports. A 46-year-old right-handed woman was referred for an esophagogastroscopy and pH monitoring for dysphagia and heartburn. Midazolam (6 mg) and fentanyl (50 μg) were used sequentially IV for sedation and analgesia. Following the procedure, the patient failed to regain consciousness, even after naloxone administration. She was transferred to an intensive care unit where she remained stable, without signs of respiratory or circulatory insufficiency, but unconscious for 48 hours. When she regained consciousness, the neurologic examination revealed horizontal nystagmus, impaired swallowing, right facial weakness, right hemihypesthesia, and right hemiparesis (upper limb 2 to 3/5, lower limb 0 to 1/5). She had a generalized, throbbing, severe (9 to 10/10 in a verbal rating scale) headache, accompanied by nausea, vomiting, photophobia, and phonophobia. Standard cranial CT and MR scans revealed only a previously identified small lacunar infarct in the right internal capsule. Routine blood tests were normal.

The right hemiparesis and the other neurologic symptoms slowly improved with physiotherapy. Nausea was treated with domperidone (10 mg PO) and granisetron (2 mg IV) as needed. Headaches required daily treatment for 6 weeks, with aspirin (1 mg IV), indomethacin (100 mg PR), or chlorpromazine (25 mg PO), and finally subsided after prednisolone (3-day course of 60 mg PO). She was discharged from hospital care 50 days after admission headache-free and having regained full limb power.

Her previous medical history was positive for recurrent episodes compatible with hemiplegic migraine attacks since age 16. Her past surgical history included multiple procedures that occurred uneventfully (table). Her family history was positive for migraine without aura in her paternal grandfather.

The patient had started prophylactic migraine therapy with the atypical calcium channel modulator flunarizine (10 mg daily) 2 years previously, and her attack frequency decreased from weekly to one every other month. She was able to abort her attacks during the aura period with ketamine (25 to 50 mg, nasal spray). At the time of admission, she was also taking propanolol

Table *Case reports on hemiplegic migraine crises precipitated by sedation/anesthesia*

Ref.	Patient	Past medical/ surgical history	Procedure	Drugs used*	Clinical and laboratory features	Recovery
4	30-y-old woman	Removal of ganglion cyst (hand), bilateral tubal ligation, history of "prolonged recovery" from anesthesia, codeine allergy (rash), recurrent headache (never had hemiparesis)	Extraction of four partially impacted third molars (wisdom teeth)	Fentanyl 0.1 mg, midazolam 2.5 mg	Left hemiparesis, severe headache, normal brain CT, EEG, and lumbar puncture	Motor function: 5th d, headache persisted <6 wk
5	33-y-old woman	Familial hemiplegic migraine, appendectomy, dilation and curettage	Diagnostic laparoscopy for central abdominal pain and dyspareunia	Propofol 170 mg, alfentanyl 0.5 mg, atropine 0.6 mg, vecuronium 3 mg, morphine 10 mg, diclofenac 100 mg, nitrous oxide + enflurane	Gross power deficit four limbs (left > right), left hemiparesis (next day), without headache, normal brain MRI	Motor function: 48 h
Current report	46-y-old woman	Sporadic hemiplegic migraine, tracheal stenosis, restrictive lung disease Critical illness polyneuropathy, tonsillectomy and adenoidectomy, appendectomy, cholecystectomy, wisdom teeth extractions, dilation and curettage, knee arthroscopy	Esophagogastroscopy and pH monitoring for dysphagia and heartburn	Midazolam 6 mg, fentanyl 50 μg	Coma, right hemiparesis and hemisensory loss, horizontal nystagmus, reduced swallowing, migraine, headache, brain CT and MR scans without acute changes	Motor function: 43 d, headache: 49 d

* All except for nitrous oxide and enflurane were given IV.

80 mg/day for occasional orgasmic headache, omeprazole 20 mg/day for heartburn, and aspirin 75 mg/day for secondary stroke prophylaxis, and she had been attack-free for 14 weeks.

Discussion. In this patient with sporadic hemiplegic migraine, a hemiplegic migraine attack was triggered by sedation with midazolam and fentanyl for a routine esophagogastroscopy. We found two similar cases.[2,3] The possibility that this episode was precipitated by the stress of the procedure itself cannot be excluded, as patients with familial hemiplegic migraine are susceptible to minor stressful events such as mild head trauma.[4] The common drug used for sedation in all three patients was the opioid fentanyl or alfentanyl.

Aura is believed to be a consequence of cortical spreading depression,[5] which is mediated by excitatory amino acids and can be blocked by NMDA receptor antagonists such as ketamine, with clinical benefit.[6] There is evidence that microinjection of opioid peptides into the neocortex and hippocampus of experimental animals can elicit cortical spreading depression.[7]

We cannot be certain whether these reports represent a mere coincidence or if opioids used in sedation or anesthesia can trigger severe hemiplegia in patients with hemiplegic migraine. The aim of this report is to generate feedback from colleagues so that new cases may be collected and further analysis performed. This will, it is hoped, enable us to identify shared risks of drugs and/or procedures in patients with hemiplegic migraine and consider the potential protective role of other drugs for their anesthesia, such as ketamine.[6] In this way, it should be possible to establish recommendations for neurologists and anesthetists when dealing with hemiplegic migraine patients facing an anesthetic event.

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References

1. Moskowitz MA, Bolay H, Dalkara T. Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol 2004;55:276–280.
2. Strauss RA, Eschenroeder TA. Hemiplegic migraine following third molar extractions under intravenous sedation: report of a case. J Oral Maxillofac Surg 1989;47:184–186.
3. Thurlow JA. Hemiplegia following general anaesthesia: an unusual presentation of migraine. Eur J Anaesthesiol 1998;15:610–612.
4. Kors E, Terwindt GM, Vermuulen FLMG, et al. Delayed cerebral edema and fatal coma after minor head trauma: the role of CACNA1A calcium channel subunit gene and the relationship with familial hemiplegic migraine. Ann Neurol 2001;49:753–760.
5. Hadjikhani N, Sachez del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA 2001;98:4687–4692.
6. Kaube H, Herzog J, Kaufer T, Dichgans M, Diener HC. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. Neurology 2000;55:139–141.
7. Sprik U, Oitzl MS, Ornstein K, Huston JP. Spreading depression induced by microinjection of encephalins into the hippocampus and neocortex. Brain Res 1981;210:243–252.

Oxcarbazepine in glossopharyngeal neuralgia: Clinical response and effect on serum lipids

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A 51-year-old generally healthy woman presented with a 7-year history of frequent attacks of sharp, stabbing, and shooting pain localized in the throat radiating to the right ear. Attacks were regularly triggered by swallowing and sometimes by straining the voice for periods of days and weeks. Pain paroxysms lasted from 8 to 40 seconds, and continuous series of paroxysms lasted for more than 5 minutes. She had no sensory or motor deficits of the IXth nerve or presence of any other focal neurologic signs. Cranial CT and MR imaging did not reveal any abnormality intracranially at the base of the skull or retropharyngeally. Duplex sonography of the carotid artery was also unremarkable. A diagnosis of glossopharyngeal neuralgia was made and the patient was started on 300 mg carbamazepine (CBZ). This resulted in complete relief at a daily dose of 1,200 mg. After 6 years of therapy, routine laboratory checks demonstrated increased total cholesterol (TC) (299 mg/dL), low-density lipoprotein (LDL) (165 mg/dL), and high-density lipoprotein (HDL) (92 mg/dL) (table), even though the patient kept to a diet with low cholesterol.

Hypercholesterolemia seemed to be related to CBZ therapy. She was successfully switched to oxcarbazepine (OXC) and has remained pain-free on a daily dose of 1,500 mg. Total serum cholesterol concentration as well as LDL cholesterol levels decreased to normal values after 3 months and have been stable for the last 18 months. No clinically relevant change was noted in serum HDL cholesterol (see the table).

Discussion. Glossopharyngeal neuralgia (GPN) is a rare form of pain compared to trigeminal neuralgia (TGN) (0.2 to 1.3% of cases of facial).[1] It is characterized by paroxysms of severe, stabbing, recurrent pain in the distribution of the glossopharyngeal nerve, ear, tonsil, larynx, and tongue in decreasing order of frequency. The location of the pain is essential to differentiate this neuralgia from the more common trigeminal neuralgia. Some accompanying symptoms have been described, particularly seizure and syncope.[2]

If treatment with drugs is unsuccessful, or there are adverse effects, surgery may be necessary. Carbamazepine is the drug of choice in the management of TGN and it has proved useful in treating GPN.[3]

CBZ-related cholesterol changes have been attributed to the induction of the hepatic P450 enzyme system by the drug.[4] Microsomal enzyme inducing drugs such as phenytoin, phenobarbital, and CBZ, and also alcohol, influence serum lipid and apoprotein concentrations. The inducers increase the concentrations of hepatic microsomal enzyme and apo A-1 mRNA, and also proteins and phospholipids. They similarly influence HDL/LDL ratio. OXC, a keto-derivative of CBZ, is a new AED that closely resembles CBZ in structure. However, it has a different metabolic pathway in the liver; instead of by oxidation, it is mainly metabolized by reduction, and does not appear to induce the oxidative P450-enzyme system to the same extent as CBZ. Liver P450 enzyme system induction and serum lipid levels were evaluated in a prospective follow-up study in 12 men with epilepsy after replacing CBZ with OXC.[5] Antipyrine half-life increased and antipyrine clearance decreased 2 months after the medication was changed, reflecting normalization of liver P450.

Early open-label studies have investigated the role of OXC in trigeminal neuralgia refractory to CBZ[6] and the results showed the drug to have excellent efficacy. The safety data suggest that OXC may be associated with improved compliance compared with CBZ, as OXC was well tolerated with few significant adverse events, even in patients who could not tolerate CBZ.

A recent animal study reported that the inhibition of substance P-mediated pain transmission may be involved in the antinociceptive action of OXC.[7]

Previous studies in patients with epilepsy have also shown that the CBZ-induced changes in metabolic function, like hyperlipidemia, equilibrate after CBZ is replaced with OXC.[5]

We do not have a lipid profile of our patient before CBZ treatment. However, a stable low cholesterol diet, exercise program, and eating behavior before and after the switch, as well as timing of blood draw after an overnight fast in all examinations, suggest that CBZ is the cause of hypercholesterinemia and prompted the switch to OXC.

Table *Cholesterol levels in the patient*

Cholesterol	CBZ	OXC after 3 mo treatment	OXC after 18 mo treatment
Total, mg/dL	299	223	218
LDL, mg/dL	160	124	110
HDL, mg/dL	92	86	85

CBZ = carbamazepine; OXC = oxcarbazepine; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

OXC may be the preferable drug with regard to the effects of the medication on lipid metabolism.

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References

1. Katusic S, Williams DB, Beard CM, et al. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945–1984. Neuroepidemiology 1991;10:276–281.
2. Galetta SL, Raps EC, Hurst RW, et al. Glossopharyngeal neuralgia from a posterior fossa arteriovenous malformation. Neurology 1993;43:1854–1855.
3. Minagar A, Sheremata WA. Glossopharyngeal neuralgia and MS. Neurology 2000;54:1368–1370.
4. Eiris JM, Lojo S, Del Rio MC, et al. Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy. Neurology 1995;45:1155–1157.
5. Isojärvi JIT, Pakarinen AJ, Rautio A, et al. Liver enzyme induction and serum lipid levels after replacement of carbamazepine with oxcarbazepine. Epilepsia 1994;35:1217–1220.
6. Zakrzewska JM, Patsalos PN. Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia. J Neurol Neurosurg Psychiatry 1989;52:472–476.
7. Kiguchi S, Imamura T, Ichikawa K, et al. Oxcarbazepine antinociception in animals with inflammatory pain or painful diabetic neuropathy. Clin Exp Pharmacol Physiol 2004;31:57–54.

T2-hyperintense cerebellar cortex in Marinesco–Sjögren syndrome

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Hyperintensity of the cerebellar cortex on T2-weighted images is a rare finding and has been considered pathognomonic for infantile neuroaxonal dystrophy (INAD).[1] However, we present three children with Marinesco–Sjögren syndrome (MSS; OMIM 248800) and hyperintense cerebellar cortex on MRI. Additional findings were widened cerebellar fissures, an enlarged fourth ventricle, reduced *N*-acetylaspartate, and elevated myo-inositol on ^{1}H-MR spectroscopy (MRS) of the cerebellum.

Patients and methods. Patients. Patient 1 is the 5-year-old son of consanguineous parents; Patients 2 (girl, age 7 years) and 3 (boy, age 14 months) are siblings of nonconsanguineous parents. Hypotonia, developmental delay, strabismus, and short stature were present in all patients. Ataxia was present in Patients 1 and 2. Tendon reflexes were normal, and pyramidal tract signs were absent. Bilateral cataracts were diagnosed in Patient 1 (age 4.5 years) and Patient 2 (age 6.8 years). At age 14 months, cataracts had not yet developed in Patient 3.

Serum creatine (Cr) kinase levels were normal in Patient 1 and slightly elevated in Patients 2 and 3. Extensive biochemical and metabolic screening was normal.

EMG disclosed a myopathic pattern. Biopsied muscle from Patients 1 and 2 showed autophagic vacuoles on light microscopy. Electron microscopy revealed characteristic dense membranous structures associated with the nuclei.[2]

MRI and spectroscopy. MRI (0.5 and 1.5 T) was performed at age 5.6 years in Patient 1, at ages 15 months and 7 years in Patient 2, and at age 14 months in Patient 3. Short echo time, single voxel spectra (1.5 T; stimulated-echo acquisition mode: echo time, 20 ms; repetition time, 1,500 ms; number of signal acquisitions = 256; MOIST water suppression) were obtained from basal ganglia, parieto-occipital white matter, and cerebellum in Patients

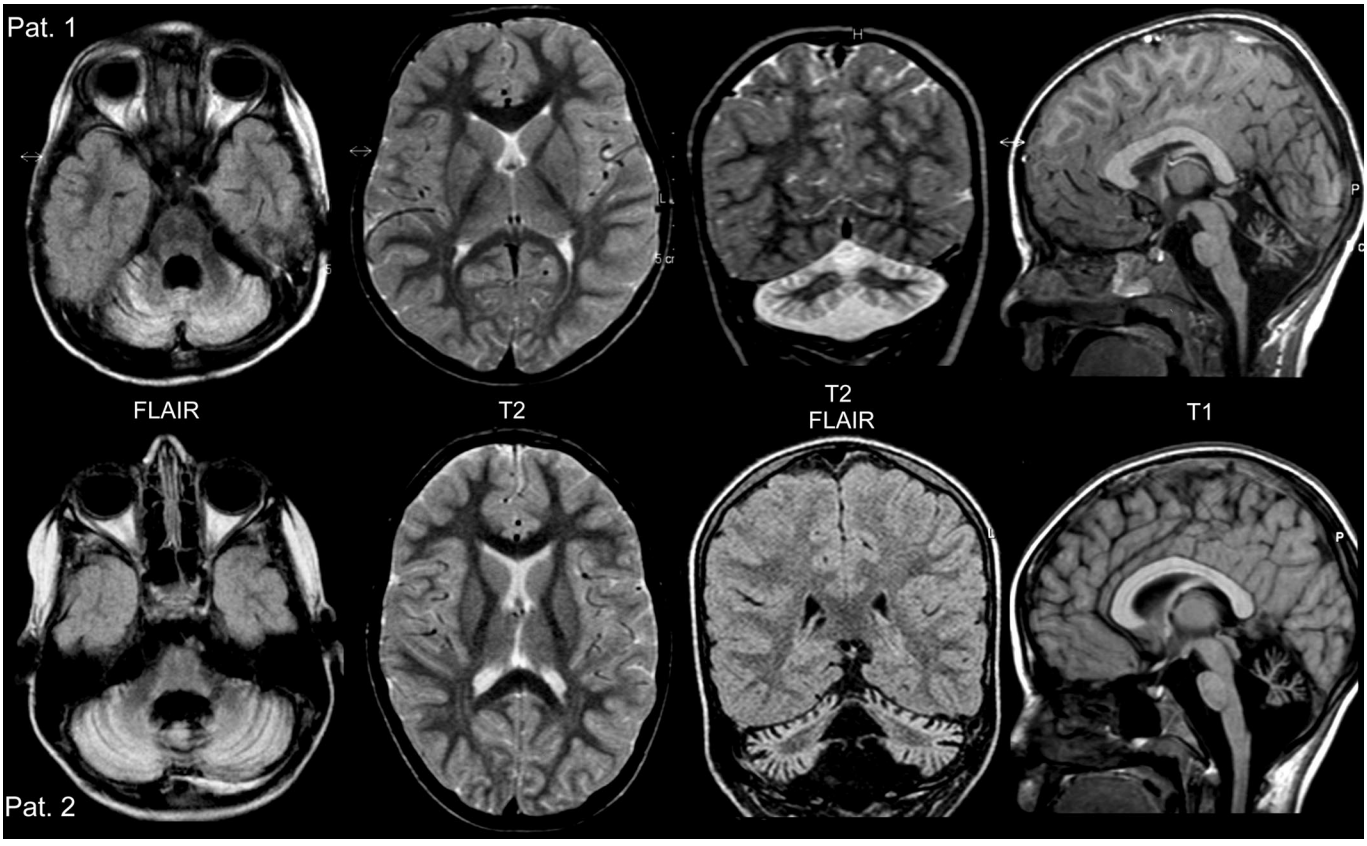

Figure. MRI of Patients 1 and 2 demonstrates hyperintensity of the cerebellar cortex, widened cerebellar fissures, and an enlarged fourth ventricle in the absence of basal ganglia changes.

1 and 2. Using the LCModel postprocessing software (S. Provencher Inc., Ontario, Canada), metabolite ratios were compared with data from 11 healthy volunteers.

Results. Hyperintensity of the cerebellar cortex on T2-weighted and fluid-attenuated inversion recovery images was the most striking finding on MRI. Cerebellar foliation was normal. Cerebellar tissue was reduced with widening of the cerebellar fissures, most pronounced in the vermis, and enlargement of the fourth ventricle. The brainstem and the size of the posterior fossa appeared normal. No white matter abnormalities were observed, and myelination was normal for age. The basal ganglia, cerebral cortex, and pituitary gland were also normal (figure). MRI changes in Patient 2 were not progressive.

MRS revealed reduced *N*-acetylaspartate/Cr (mean ± SD, 0.36 and 0.49 vs 1.36 ± 0.18 in controls) and increased myo-inositol/Cr (1.46 and 1.47 vs 0.72 ± 0.15) metabolite ratios in the cerebellum. In Patient 2, myo-inositol/Cr was also elevated in the parieto-occipital white matter (1.13 vs 0.65 ± 0.09). Basal ganglia spectra were normal.

Discussion. Although hyperintense cerebellar cortex in combination with extensive white matter changes was recently described in a patient with a mitochondrial disorder,[3] hyperintensity of the cerebellar cortex is the neuroradiologic hallmark of INAD and considered pathognomonic for this disorder.[1] INAD is a rare autosomal-recessive disorder involving CNS fiber tracts and peripheral axons. Clinically, it is characterized by infantile onset and rapid progression of psychomotor regression and hypotonia, evolving spasticity, and visual disturbance caused by optic atrophy.

In contrast, our patients had nonprogressive psychomotor retardation, ataxia, and cataracts, suggesting the diagnosis of MSS. Other frequent features of MSS include muscle hypotonia, muscle weakness and atrophy, and a short stature. Hypogonadism observed in some patients has been correlated with a small or absent pituitary gland on MRI. Skeletal anomalies with scoliosis and chest and foot deformities have also been reported. Diagnosis is based on typical clinical findings, the presence of autophagic vacuoles, and unique dense membranous structures associated with cell nuclei in biopsied muscle.[2] These were all demonstrated in our patients.

Cerebellar changes, more pronounced in the vermis than the hemispheres, are the most common imaging finding in MSS.[4-7] Variably described as hypoplasia or atrophy, they consist of either a small, compact cerebellum without widened fissures[6] or a normally sized cerebellum with wide fissures and an enlarged fourth ventricle.[4,6,7] Additional findings are absence of the posterior bright spot and/or a small anterior pituitary gland,[6] supratentorial white matter abnormalities, and cerebral atrophy, the latter more commonly observed in adolescent and adult patients.[5,6]

Apart from the additional finding of a distinctly hyperintense cerebellar cortex, the cerebellar changes in our patients were consistent with the findings reported in MSS, namely, nonprogressively widened cerebellar fissures and an enlarged fourth ventricle within a normal bony posterior fossa.

Interestingly, on histopathology there is severe atrophy of the cerebellar cortex with neuronal loss and astrogliosis in MSS and INAD. This similarity of underlying histopathologic changes may explain the occurrence of a T2-hyperintense cerebellar cortex in the two diseases.

In conclusion, hyperintensity of the cerebellar cortex on T2-weighted images is not pathognomonic for INAD but also can be a characteristic finding of MSS.

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References

1. Steinlin M, Blaser S, Boltshauser E. Cerebellar involvement in metabolic disorders: a pattern-recognition approach. Neuroradiology 1998;40:347–354.
2. Sewry CA, Voit T, Dubowitz V. Myopathy with unique ultrastructural feature in Marinesco-Sjögren syndrome. Ann Neurol 1988;24:576–580.
3. Wolf NI, Seitz A, Harting I, et al. New pattern of brain MRI lesions in isolated complex I deficiency. Neuropediatrics 2003;34:156–159.
4. Georgy BA, Snow RD, Brogdon BG, Wertelecki W. Neuroradiologic findings in Marinesco-Sjögren syndrome. AJNR Am J Neuroradiol 1998;19:281–283.
5. Reinhold A, Scheer I, Lehmann R, et al. MR imaging features in Marinesco-Sjögren syndrome: severe cerebellar atrophy is not an obligatory finding. AJNR Am J Neuroradiol 2003;24:825–828.
6. McLaughlin JF, Pagon RA, Weinberger E, Haas JE. Marinesco-Sjögren syndrome: clinical and magnetic resonance imaging features in three children. Dev Med Child Neurol 1996;38:636–644.
7. Katafuchi Y, Kosai K, Ohtaki E, et al. Cerebral cortex and brainstem involvement in Marinesco-Sjögren syndrome. Ann Neurol 1990;27:448–449.

Dental diplopia with transient abducens palsy

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Diplopia is uncommon after intraoral local anesthesia for dental procedures.[1-7]

Case report. A healthy 29-year-old man was examined at a hospital-based dental clinic several days after sustaining mild facial trauma during a snow skiing accident. He had dental pain and thermal sensitivity, which related to fractured cusps of the bottom right second premolar tooth (no. 29). Because of the severity of the cusp fracture, the treatment plan was to remove this tooth. The patient's medical history was otherwise unremarkable, and he denied any allergies. The dentist proceeded to anesthetize the patient with a right inferior alveolar nerve block using a standard 25-gauge needle (1.5 inches) and 1.8 mL of 2% lidocaine with 1:100,000 epinephrine. No other anesthetic or analgesic was used during this procedure. Initial aspiration of the needle was devoid of blood, but the patient did note a brief twinge in his right lower lip at the time of the injection. Within 5 minutes of the injection, profound anesthesia was obtained in the expected distribution of the inferior alveolar nerve. Shortly thereafter and before the procedure began, the patient had new-onset diplopia with rightward gaze. The dentist performing the procedure observed disconjugate eye movements and transferred the patient to the emergency department. Further history revealed that the patient had previously undergone multiple dental procedures without complication and had no previous adverse reactions to anesthetics or other medications. The general examination was unremarkable, and neurologic examination was abnormal only for numbness in the distribution of the inferior alveolar nerve, esotropia, and inability to fully abduct the right eye. The remainder of extraocular movements and other cranial nerves were normal, and Horner syndrome was not present. Within ~1 hour of onset, the numbness and diplopia resolved, and the patient returned to his premorbid state.

Discussion. Ophthalmoplegia after intraoral, local dental anesthesia has been well described in the dental literature[1-7] and commonly manifests as transient abducens palsy as in our patient. The mechanism of the ophthalmoplegia is uncertain, although the route through the pterygopalatine fossa is likely because it is the only vascular-rich structure between the injection site and the abducens nerve. Extravascular spread of the anesthetic could have occurred along a dural plane anywhere near the injection site. The anesthetic could have diffused across the pterygopalatine fossa and reached the laterally located abducens nerve via the anterolateral extension of the inferior orbital fissure. Involvement of other cranial nerves serving eye movements and pupils would be more difficult to explain with this mechanism than the others.

Intravascular injection could have occurred despite careful aspiration before the administration of anesthetic. Aberrant arterial patterns and retrograde flow have been suggested to explain how the anesthetic could access structures necessary to produce ophthalmoplegia after an intra-arterial injection. Perhaps more

likely, the anesthetic could have gained access to nervous system structures in the cavernous sinus because of IV injection or absorption. As has been proposed for some infections, local anesthetic could have drained into the pterygoid venous plexus and thereby into the cavernous sinus via emissary veins traversing bony foramina, especially when the patient is in the recumbent position. Here the abducens nerve may be more susceptible than other cranial nerves because it courses through the cavernous sinus rather than in its wall, like other cranial nerves. Features of Horner syndrome seen in some patients[7] could also be explained by the anesthetic affecting sympathetic fibers that accompany the carotid artery through the cavernous sinus.

Fortunately, the anesthetic effects of lidocaine are short lived, and permanent abducens palsy has not been reported in this setting. Management is usually supportive, but a protracted course, as previously described,[4] should prompt neuro-ophthalmologic evaluation. Undaunted by his episode of diplopia, the patient returned to the dental clinic later the same day to resume treatment, which involved repeat inferior alveolar nerve block. No further incidents occurred at the time of treatment or on follow-up evaluation.

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References

1. Cooley RL, Cottingham AJ Jr. Ocular complications from local anesthetic injections. Gen Dent 1979;27:40–43.
2. Sved AM, Wong JD, Donkor P, et al. Complications associated with maxillary nerve block anaesthesia via the greater palatine canal. Aust Dent J 1992;37:340–345.
3. Marinho RO. Abducent nerve palsy following dental local analgesia. Br Dent J 1995;179:69–70.
4. van der Bijl P, Lamb TL. Prolonged diplopia following a mandibular block injection. Anesth Prog 1996;43:116–117.
5. Goldenberg AS. Transient diplopia as a result of block injections. Mandibular and posterior superior alveolar. NY State Dent J 1997;63:29–31.
6. van der Bijl P, Meyer D. Ocular complications of dental local anaesthesia. SADJ 1998;53:235–238.
7. Penarrocha-Diago M, Sanchis-Bielsa JM. Ophthalmologic complications after intraoral local anesthesia with articaine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:21–24.

Postpartum obturator neuropathy

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Case report. A previously well 34-year-old woman sought treatment postpartum for left leg weakness. Several hours after labor onset, pain was noticed in the left groin and medial thigh. Epidural anesthesia was commenced via the L3/L4 interspace. The pain resolved within 15 minutes. A deep transverse arrest occurred, and semi-urgent cesarean section was performed without complication. Difficulty in left leg adduction was apparent the following day with walking requiring assistance. Bladder, bowel, and contralateral leg function were normal.

Examination revealed profound weakness of left thigh adduction only. Knee and ankle reflexes were normal bilaterally with flexor plantar responses. The left adductor reflex was significantly reduced, whereas the right was easily elicited. A small area of decreased pinprick sensation was present over the medial left thigh. MRI of the lumbosacral spine was performed 5 days postpartum with no evidence of lumbar nerve root compression.

Three weeks later, significant weakness of left thigh adduction remained. The adductor reflex was more symmetric, and sensation was normal. Routine nerve conduction studies were normal. EMG revealed active denervation in the left adductor magnus with no motor units under voluntary activation. Other muscles innervated by the left L2 to L4 nerve roots were normal. MRI of the pelvis and thigh demonstrated increased signal on T2-weighted images in the adductor brevis, obturator externus, and adductor magnus muscles, consistent with denervation (figure). No focal compressive lesion or signal change within the obturator nerve was seen.

Discussion. The obturator nerve is formed by fibers from the ventral divisions of the second, third, and fourth lumbar nerves.[1] As the nerve crosses the upper margin of the obturator internus muscle, it is vulnerable to compression against the lateral wall of the pelvis. The nerve then curves downward and forward around the lateral wall to traverse the obturator foramen. Within this foramen, the nerve divides into anterior and posterior branches. The anterior division innervates the adductor longus, gracilis, and adductor brevis muscles and gives off sensory branches to the medial thigh. The posterior division innervates obturator externus and adductor magnus.

Obturator neuropathy causes weakness of thigh adduction as the only motor manifestation because other nonobturator-innervated muscles participate in lateral hip rotation. Medial thigh pain can occur and may radiate toward the knee. Altered sensation typically occurs over the medial aspect of the mid and lower thigh. Complete loss of sensation is unusual because of overlap from neighboring cutaneous nerves, and occasionally there is no sensory loss. In chronic cases, wasting of the medial thigh is seen. During ambulation, the hip is abnormally abducted, resulting in a circumducting, wide-based gait. Ipsilateral loss of the hip adductor tendon reflex can suggest obturator neuropathy; however, because it is sometimes absent in healthy people, the contralateral reflex must be easily elicited for the finding to be useful.

Obturator nerve lesions are uncommon, primarily because of its protected location deep within the pelvis and medial thigh.

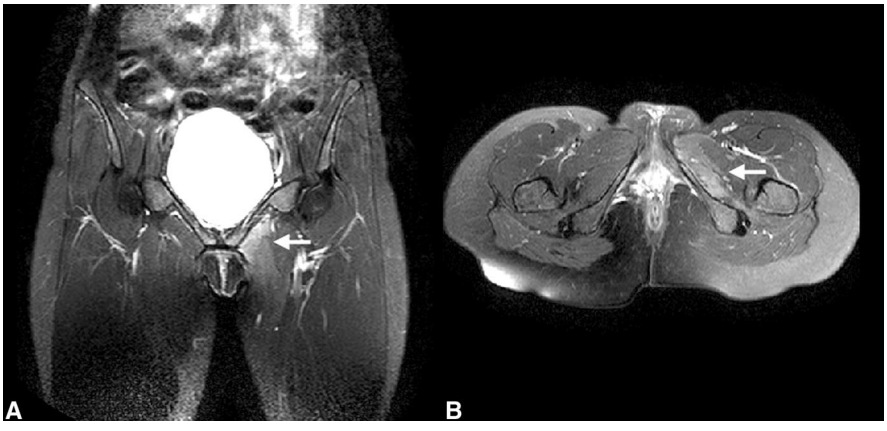

Figure. Coronal (A) and axial (B) fat-suppressed T2-weighted MRIs of the upper thigh showing increased signal within the adductor brevis and adductor magnus on the left (arrows). Atrophy of these muscles is also evident.

Although most cases are isolated reports, a recent series of 22 patients collected during a 24-year period was published with clinical outcomes.[2] Common etiologies included total hip arthroplasty, pelvic surgery, and pelvic trauma. Regardless of the cause and the severity of the lesion, most acute obturator neuropathies recovered well with conservative management. Recovery for chronic obturator neuropathy was generally poor and depended on the underlying systemic disease.[2]

Injury during pregnancy or parturition is well described for most lower limb nerves.[3] The femoral nerve is most commonly affected. Lumbosacral plexus injuries can be confused with disc herniation, typically occurring in fetal-pelvic disproportion or instrumentation-assisted delivery. The increasing use of regional anesthesia can "mask" sensory symptoms. Positioning of the patient can also contribute to nerve injury, with the lithotomy position leading to abnormal angulation of the obturator nerve as it leaves its foramen.

Obturator neuropathy after vaginal delivery has been rarely reported. Sorenson et al.[2] had one such case in a series of 22 patients, and only a handful of isolated case reports are found in the literature.[4-6] Most underwent EMG, but none reported the use of MRI.

Investigation of peripheral nerve injury depends predominantly on EMG, which provides diagnostic and prognostic information. Nerve conduction studies are limited when nerves are located deep to surface-recording electrodes or when Wallerian degeneration is incomplete. MRI is becoming increasingly used to demonstrate denervated skeletal muscle with increased signal on T2-weighted and short T1 (time to inversion) recovery sequences.[7] MRI can also identify individual nerves and nerve roots, looking for focal compression or evidence of demyelination.

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References

1. Sunderland S. Obturator nerve. In: Sunderland S, ed. Nerves and nerve injuries, 2nd ed. London: Churchill and Livingstone, 1990:992–998.
2. Sorenson EJ, Chen JJ, Daube JR. Obturator neuropathy: causes and outcome. Muscle Nerve 2002;25:605–607.
3. Reynolds F. Maternal sequelae of childbirth. Br J Anaesth 1995;75:500–501.
4. Haas DM, Meadows RS, Cottrell R, Stone WJ. Postpartum obturator neuropraxia: a case report. J Reprod Med 2003;48:469–470.
5. Lindner A, Schulte-Mattler W, Zierz S. Postpartales Nervus obturatorius-Syndrom: Fallbericht und Ubersicht uber die Nervenkompressionssyndrome wahrend Schwangerschaft und Geburt. Zentralbl Gynakol 1997;119:93–99.
6. Warfield CA. Obturator neuropathy after forceps delivery. Obstet Gynecol 1984;64(suppl 3):47S–48S.
7. McDonald CM, Carter GT, Fritz RC, Anderson MW, Abresch RT, Kilmer DD. Magnetic resonance imaging of denervated muscle: comparison to electromyography. Muscle Nerve 2000;23:1431–1434.

Leber hereditary optic neuropathy with chorea and dementia resembling Huntington disease

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Leber hereditary optic neuropathy (LHON) is a mitochondrial disease characterized by acute or subacute bilateral visual loss usually in young men. However, LHON also occurs in those with other neurologic abnormalities,[1] such as epilepsy, peripheral neuropathy, tremor, dementia, dystonia, parkinsonism, and multiple sclerosis–like illness. The disease in those patients has been called "Leber plus."[2] We report a patient with Leber plus associated with chorea and dementia resembling Huntington disease (HD).

Case report. A 37-year-old woman sought treatment for choreic movement and mental deterioration. She developed normally and had relatively good grades in school. At age 24 years, she showed an involuntary movement in her hands and became restless and negligent of housekeeping. At approximately age 30 years, her choreic movement spread to the upper extremities and trunk. By age 34 years, she was unable to walk or do most housekeeping tasks. She also became forgetful and made more errors on tasks that required concentration. At age 35 years, she was first examined by a neurologist and diagnosed with HD by the results of neurologic examinations and imaging studies (MRI and SPECT). She was then treated with haloperidol, but her disease worsened progressively. Shortly after the first diagnosis as HD, she was referred to our hospital at age 37 years.

Her brother and one of her maternal uncles had visual loss caused by bilateral optic neuropathy, and 11778G>A mutation was confirmed by mitochondrial DNA (mtDNA) analysis in her uncle. No other family members exhibited any neurologic abnormalities.

On neurologic examination, severe impairments in memory and attention were noted (Mini-Mental State Examination score, 13/30). Her vision and visual field were normal, and there was no evidence of optic atrophy.

Motor and sensory tests were normal without motor impersistence and hypotonia in lower limbs. Cerebellar function tests were normal. The most striking feature of the patient was remarkable choreic movements, which were observed in the upper and lower limbs, trunk, and face as shaking head, bending trunk, swinging arms up, facial grimacing, and irregular flexion of legs. Her gait was disturbed because of involuntary movements of legs.

Routine laboratory examinations were normal. No acanthocytes were found in the peripheral blood smear. There was no evidence of Wilson disease or mitochondrial cytopathy. Brain MRI revealed atrophy of the head of the caudate nucleus and occipital and parietal cortices (figure). SPECT using a tracer of ^{99m}Tc-

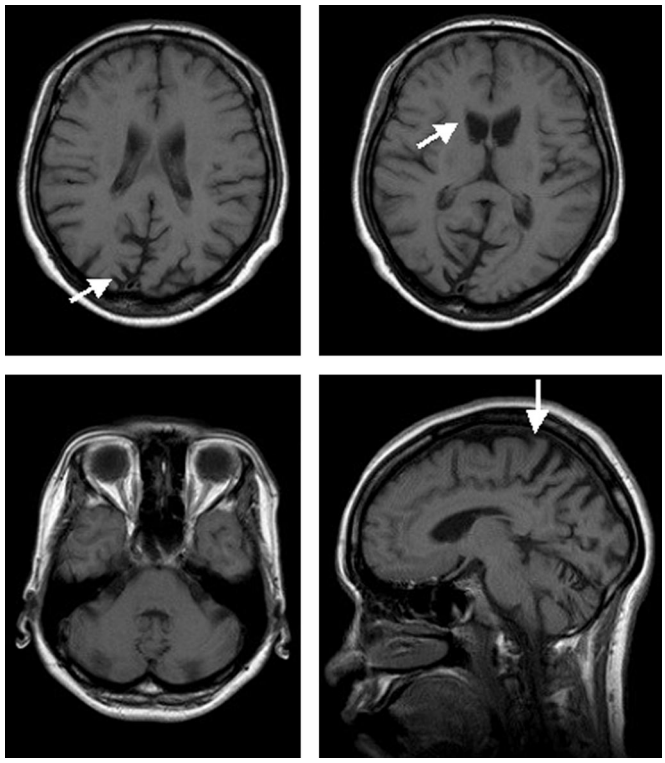

Figure. MRI scan demonstrates slight atrophy in the head of the caudate nucleus. Cerebral cortex of the occipital and parietal lobes also is atrophic.

ethylcysteinate dimer demonstrated decrease of blood flow in the basal ganglia and occipital and parietal lobes. EEG showed a basal activity of 9 Hz with occipital dominancy.

DNA analysis was performed using genomic DNA extracted from the peripheral leukocytes after obtaining informed consent. Although no repeat expansions were found in huntingtin for HD or in atrophin-1 for dentatorubral pallidoluysian atrophy (DRPLA), the G-to-A transition mutation was detected at nucleotide 11778 in the *ND4* gene of mtDNA, which is known to be responsible for LHON.

Discussion. The patient showed choreic movements with hypotonia and severe dementia similar to HD. However, the results of repeated genetic analyses for HD were all negative, whereas the 11778G>A mutation in mtDNA responsible for LHON was detected. Additionally, two of her family members were clinically and genetically diagnosed with LHON, although they did not show HD-like involuntary movement. This patient's choreic movement and dementia were predominant clinical features, whereas there was no optic atrophy suggestive of LHON. Negative results of gene analysis for HD and DRPLA suggest that chorea and dementia of this patient could be part of the symptoms of Leber plus, similar to a rare case of LHON with movement disorders.[3] Because symptoms of Leber plus were variable even in the same family,[4,5] visual loss in her brother and uncle also supports that this patient may have a variant phenotype of Leber plus. Chorea and dementia reminiscent of HD are rare in LHON associated with a 11778G>A mutation, whereas dystonia was reported to accompany Leber plus with a 14459G>A, 11696A>G, or 14596T>A mutation.[5] In etiology, peripapillary microangiopathy is thought to be one of the main pathologic findings of LHON.[1] Microangiopathy may also involve other parts of the CNS and cause the various neurologic symptoms observed in Leber plus.

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References

1. Nikoskelainen EK, Marttila RJ, Huoponen K, et al. Leber's "plus": neurological abnormalities in patients with Leber's hereditary optic neuropathy. J Neurol Neurosurg Psychiatry 1995;59:160–164.
2. Newman NJ. Leber's hereditary optic neuropathy. New genetic considerations. Arch Neurol 1993;50:540–548.
3. Chariot P, Brugieres P, Eliezer-Vanerot M-C, Geny C, Binaghi M, Cesaro P. Choreic movements and MRI abnormalities in the subthalamic nuclei reversible after administration of Coenzyme Q10 and multiple vitamins in a patient with bilateral optic neuropathy. Mov Disord 1999;14:855–859.
4. Gropman A, Chen T-J, Perng C-L, et al. Variable clinical manifestation of homoplasmic G14459A mitochondrial DNA mutation. Am J Med Genet 2004;124A:377–382.
5. Tarnopolsky MA, Baker SK, Myint T, Maxner CE, Robitaille J, Robinson BH. Clinical variability in maternally inherited Leber hereditary optic neuropathy with the G14459A mutation. Am J Med Genet 2004;124A:372–376.

Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: A new clinical entity?

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Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the human CNS caused by polyomavirus JC.[1] Its characteristic pathologic features include lytic infection of oligodendrocytes, with typical nuclear inclusions, formation of large bizarre astrocytes, and demyelination. PML is common in immunosuppressed individuals and is the third most frequent neurologic complication in HIV-infected patients in the era of highly active antiretroviral therapy (HAART).[2] Except for HAART, no therapy has been demonstrated to be effective against PML; the efficacy of cidofovir, a nucleotide analogue that inhibits the replication of simian polyomavirus in vitro, is controversial.

Selected reports demonstrate that in patients with AIDS, PML can occur early after the introduction of HAART during the phase of recovery of the immune system. These cases are sometimes associated with inflammatory reaction as shown by the presence of perivascular lymphomonocytic infiltrates or contrast enhancement on neuroimaging studies and show variable clinical outcomes.[3-6] In this report, we describe the clinical and pathologic findings in a patient with AIDS-associated PML with an onset late after HAART initiation and findings of an abnormal inflammatory reaction at brain biopsy.

Case report. A 37-year-old male former injection drug user was diagnosed with HIV-1 infection in 1998 while he was asymptomatic. He had no history of autoimmune or neurologic disorders, allergy to drugs, or other relevant diseases. After 1998, he remained asymptomatic with $CD4^+$ counts permanently >400 cells/mm^3. In January 2000, because of a progressive increase of plasma HIV RNA (124,700 copies/mL), he started zidovudine, lamivudine, and indinavir; indinavir was subsequently substituted for abacavir because of intolerance. Virologic success (HIV RNA constantly <50 copies/mL) was achieved and subsequently maintained. In May 2002, although CD4 count had increased to 659 cells/mm^3, the patient began to show a progressive right arm tremor and ataxic gait. In September 2002, when the CD4 count was 1,191 cells/mm^3, he showed further worsening of the right arm tremor and abnormal gait, with dysarthria and memory deficits. Brain MRI revealed lesions at the left frontal and posterior parietal lobes, hyperintense on T2-weighted images. A repeat MRI in December showed an increase in the size of the lesions (figure, A).

PCR analysis of CSF for JC virus (JCV), *Toxoplasma* Epstein–Barr virus, herpes virus, varicella-zoster virus, and cytomegalovirus DNA, as well as research for oligoclonal bands, was repeatedly negative; HIV RNA in CSF was <20 copies/mL. Because of clinical and radiologic progression, in January 2003 an open-air brain biopsy of the parietal brain lesion was performed. The pathologic picture (figure, B through D) revealed demyelination foci, several oligodendrocytes showing enlarged nuclei and rare "bizarre" astrocytes. The surrounding tissue showed a diffuse perivascular inflammatory infiltrate consisting of lymphocytes, macrophages ($LN5^+$), and some plasma cells, with focal microthromboangiopathy. Immunohistochemistry (IHC) with anti-SV40 revealed a cross-reactive nuclear positivity in oligodendrocytes; there was no sign of other infection, including HIV (negative HIV p24 antigen by IHC). Nested PCR performed on DNA extracted from brain tissue using JCV-specific primers was positive.[7] The patient was started on cidofovir (5 mg/kg every 2 weeks for a total of four cycles) and prednisone (2 mg/kg/d). From February 2003 onward, the patient refused any kind of treatment. No apparent beneficial effect from anti-inflammatory therapy was observed. In May 2003, 1 year after the onset, the patient showed a severe neurologic picture, with cognitive and psychiatric symptoms (progressively impaired memory, agitated depression, mutism) remaining stable for the last 2 months. The patient died at home in June 2003.

Discussion. Diagnostic sensitivity of PML by PCR detection of JCV in CSF was high in the pre-HAART era,[7] but exposure to HAART and a good immunologic condition might have decreased the yield of JCV in this case.

Immunologic reconstitution could be beneficial or could lead to an unfavorable outcome depending on type and entity of the inflammatory reaction. In our case, the intense immune reaction caused an irreversible neurologic degeneration. Differently from other reports of PML occurring in patients with AIDS after HAART, this case showed a late onset, 2 years after starting antiretroviral therapy. This extreme case shows how inflammatory forms of PML should be considered a new clinical entity in HIV-infected patients treated with HAART. These cases require a reformulation of the diagnostic and therapeutic approach.

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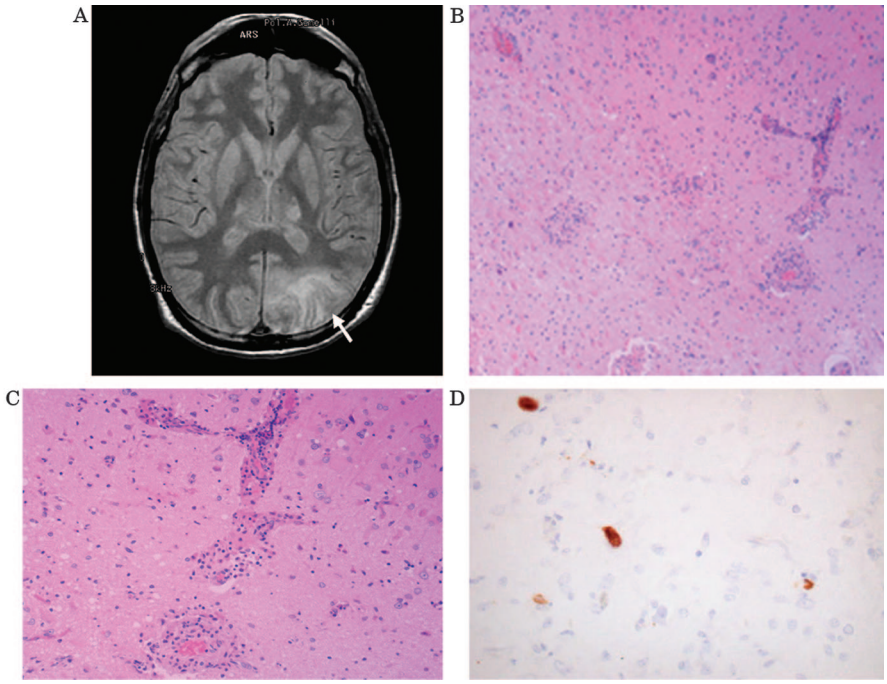

Figure. Sagittal scan of brain MRI taken in December 2002: the arrow shows the left posterior parietal lesion, hyperintense on T2-weighted imaging, without gadolinium enhancement (A). H-E stain of brain biopsy specimen showing a focal demyelinated area with perivascular inflammatory reaction consisting of mononuclear cells at low (×100, B) and higher magnification (×250, C). Immunohistochemistry with anti-SV40 antibody showing a cross-reactive nuclear positivity in infected oligodendrocytes (D).

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References

1. Berger JR, Concha M. Progressive multifocal leukoencephalopathy: the evolution of a disease once considered rare. J Neurovirol 1995;1:5–18.
2. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). J Neurovirol 2003;9(suppl 1):47–53.
3. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reaction in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. AIDS 2001;15:1900–1902.
4. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron R. Fatal immune restoration disease in human immunodeficiency virus type1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. Clin Infect Dis 2002;35:1250–1257.
5. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leukoencephalopathy with unusual inflammatory response during antiretroviral treatment. J Neurol Neurosurg Psychiatry 2003;74:1142–1144.
6. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? J Neurol 2003; 9(suppl 1):25–31.
7. De Luca A, Cingolani A, Linzalone A, et al. Improved detection of JC virus DNA in cerebrospinal fluid for diagnosis of AIDS-related progressive multifocal leukoencephalopathy. J Clin Microbiol 1996;34:1343–1346.

Myocardial infarction following brief convulsive seizures

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The CNS influences the electrical and mechanical functions of the heart.[1] Seizures can produce EKG repolarization abnormalities, arrhythmias, and perhaps myocardial injury.[2,3] Acute coronary insufficiency leading to myocardial infarction (MI) has been reported with status epilepticus and occurs rarely in association with electroconvulsive therapy (ECT).[4,5] MI has not been reported after self-limited spontaneous convulsions. We present two cases of acute coronary syndrome (ACS) with MI after generalized tonic-clonic (GTC) seizure.

Case reports. Patient 1. A 69-year-old man with a history of right frontal and occipital infarcts came to the emergency room after two witnessed GTC seizures that began with leftward eye deviation. He denied antecedent chest pain or dyspnea. After a period of postictal somnolence, he reported retrosternal chest pain. EKG showed 2-mm ST-segment depressions in leads V3 to V6. Troponin I peaked at 86 ng/mL. Nuclear stress testing suggested reversible ischemia in the left anterior descending (LAD) artery distribution. MRI of the brain showed no acute abnormalities; EEG revealed no epileptiform patterns. He was started on phenytoin for poststroke epilepsy and was lost to follow-up evaluation. Six months later, he had another witnessed GTC seizure complicated by cardiogenic shock; phenytoin level at the time of presentation was 4.3 μg/mL. Troponin I peaked at 69 ng/mL. Coronary angiography demonstrated severe three-vessel disease with plaque rupture in the LAD; he underwent uneventful coronary bypass surgery.

Patient 2. A 53-year-old man with a history of hypertension, diabetes, and alcoholism was brought to the emergency room after a witnessed GTC withdrawal seizure that occurred in a supermarket. He denied preceding cardiac symptoms and had no history of ischemic heart disease or seizures. On arousal, he reported nausea and epigastric pain. EKG showed 2-mm ST-segment elevations in leads II, III, and aVF. Coronary angiography and intravascular ultrasound revealed moderate stenosis of the LAD and a ruptured plaque in the right coronary artery without thrombus. The patient was treated medically. He ruled in for an ST-elevation MI with a peak troponin I of 223 ng/mL. Noncontrast head CT showed chronic white matter changes. EEG was normal.

Discussion. These cases demonstrate that ACS leading to MI can follow brief epileptic convulsions and provoked alcohol withdrawal seizures. Although presumably rare, the occurrence of ACS after a seizure is not surprising in patients with coronary

artery disease given the physiologic effects of a generalized convulsion on the heart.

A GTC seizure can be considered a brief physiologic cardiac stress test. Within minutes of a convulsion, plasma norepinephrine and epinephrine levels can reach 12 and 40 times normal.[6] Concomitant increases in heart rate, blood pressure, and myocardial contractility, along with augmented cardiac afterload from tonic muscle contraction, collectively increase myocardial oxygen demand. Simultaneously, ictal apnea may lead to hypoxia. The resultant mismatch between myocardial metabolic demands and oxygen delivery could produce myocardial ischemia in patients with a fixed coronary artery stenosis. The physiologic stress associated with isolated seizures may also be severe enough to produce subendocardial ischemia in the absence of coronary flow impairment.[7] Alternatively, increased coronary flow and shear stress could rupture vulnerable coronary atherosclerotic plaque, leading to MI.

Neither of the reported patients had previous cardiac symptoms; however, the functional and angiographic evidence of coronary atherosclerosis suggests a coronary etiology in both patients. In Patient 1, either supply-demand oxygen mismatch caused by a fixed coronary stenosis or coronary plaque rupture may have caused MI; because coronary angiography was not performed, the actual mechanism of injury remains unknown. Plaque rupture appears to have been the cause of the transmural MI in Patient 2 based on the angiographic findings. Sympathetically mediated neurogenic cardiac damage may also produce EKG changes and troponin elevations.[1] Although the mechanism of infarction remains uncertain in these cases, the potential for seizure-related myocardial injury needs to be recognized given the increased prevalence of epilepsy and coronary artery disease with age.

Ictal cardiac damage can occur in patients with seizure at risk for coronary artery disease. Although postictal somnolence and endotracheal intubation can delay the diagnosis of seizure-related myocardial ischemia, timely recognition of this complication can facilitate appropriate cardiac evaluation and intervention. Prospective studies of cardiac complications after isolated seizures may provide greater understanding of the various mechanisms of myocardial injury.

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References

1. Samuels MA. Neurally induced cardiac damage. Definition of the problem. Neurol Clin 1993;11:273–292.
2. Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. Epilepsia 2000;41:542–548.
3. Dixit S, Castle M, Velu RP, Swisher L, Hodge C, Jaffe AS. Cardiac involvement in patients with acute neurologic disease: confirmation with cardiac troponin I. Arch Intern Med 2000;160:3153–3158.
4. Sechi G, Dessi-Fulgheri P, Glorioso N, Volta G, Rosati G. Myocardial infarction complicating status epilepticus. Epilepsia 1985;26:572–576.
5. Hussar AE, Pachter M. Myocardial infarction and fatal coronary insufficiency during electroconvulsive therapy. JAMA 1968;204:1004–1007.
6. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. Neurology 1984;34:255–257.
7. Tigaran S, Molgaard H, McClelland R, Dam M, Jaffe AS. Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. Neurology 2003;60:492–495.