

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

Jeffrey M. Katz, MD; and Alan Z. Segal, MD

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.<sup>1</sup> According to the American Academy of Neurology (AAN) position paper,<sup>2</sup> 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.<sup>3</sup> 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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## 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.<sup>1</sup> The Multiple Sleep Latency Test (MSLT) for demonstrating hypersomnia and sleep-onset REM periods has not been standardized for children under age 8<sup>2</sup> and has limited value in pediatrics.

CSF hypocretin-1 measurements were established as a new diagnostic tool for narcolepsy–cataplexy in adults<sup>3–5</sup> but has not yet been evaluated in children.<sup>4</sup> 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.<sup>6</sup>

Hypocretin-1 was measured by direct radioimmunoassay of CSF stored at –80 °C (detection limit 40 pg/mL).<sup>7</sup> As there was no difference in the mean CSF hypocretin level between children and adults,<sup>7</sup> the levels were defined as low (<110 pg/mL), intermediate (≥110 to ≤200 pg/mL), and normal (>200 pg/mL).<sup>5</sup> 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.<sup>5</sup>

**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](http://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 $\leq$ 8 min + $\geq$ 2 SOREMPs	4	4	0	<40
MSL $\leq$ 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- $\alpha$  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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## 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.<sup>1</sup> For the etiology of TGA, four main hypotheses have been considered: TIA, epilepsy, migraine, and transient venous ischemia.<sup>1–3</sup> 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 amnesic 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 amnesic gap. Because of the initial thoracic 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-aortic 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.<sup>1</sup> 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.<sup>4</sup> However, patients with TGA have fewer thromboembolic risk factors and smaller risk of cerebral infarction compared with those with TIA.<sup>1</sup> The DWI findings provide conflicting results concerning a possible ischemic mechanism.<sup>5</sup> 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.<sup>6</sup> 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.<sup>1</sup> 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).*

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