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WHEN A SERUM TEST OVERRIDES THE CLINICAL ASSESSMENT

The clinical features of narcolepsy-cataplexy are substantially different from anti-NMDA receptor (NMDAR) encephalitis. We report a patient whose diagnosis was established only after traditional clinical assessments prevailed over a presumably abnormal serum test result.

Clinical case. A 10-year-old girl without a medical history of interest came for a second opinion regarding treatment of anti-NMDAR encephalitis. Her symptoms started 16 months earlier when she developed tiredness, irritability, episodes of falling asleep during the day, and lingual movements when doing enjoyable activities, such as playing. On 2 occasions, she had sudden falls without loss of consciousness. Blood chemistry, brain MRI, and EEG were normal. Six months after symptom onset, she was seen at a second institution, where a blood test using a live cell-based assay was reported as low positive for NMDAR antibodies. Routine CSF studies (antibodies not examined) were unremarkable. Based on this serum test, she was diagnosed with anti-NMDAR encephalitis, screened for an underlying tumor (abdominal ultrasound negative), and treated with steroids, IV immunoglobulin, and psychotherapy. Her symptoms did not improve, and she continued falling asleep at school and while playing. Nine months after symptom onset, she was seen at a third institution; repeat NMDAR antibody testing in the same laboratory was reported positive, and additional immunotherapy was recommended but not given. She continued with excessive daytime sleepiness, irritability, and mood-dependent lingual movements (video on the *Neurology*[®] Web site at Neurology.org); however, she was maintaining her grades in school, although she required a 30-minute nap during the day and a 2-hour nap after school.

At arrival to our center, 16 months after symptom onset, her family described, in addition to the above mentioned symptoms, episodes of floppy head without losing consciousness; nocturnal shouting, talking, and moving; and compulsive eating and a weight gain of 14 kg (over 97th percentile) that started before

receiving steroids. At examination, the patient was attentive and collaborative but showed childish behavior inappropriate for her age, and rapid mood swings when asked about her symptoms. She did not exhibit memory, cognitive, or language dysfunction, and there was no evidence of myoclonus or dyskinesias during the visits.

The polysomnogram revealed a total sleep time of 442 minutes, sleep efficiency 73%. Episodes of smile-like movements and bursts of EMG activity in the muscles of the face were noted during REM sleep. She had periodic leg movements during wakefulness and sleep, associated with arousals and vocalizations as if she was complaining (index of movements during sleep: 30). No sleep-disordered breathing was noted. A 5-nap multiple sleep latency test¹ showed 5 sleep-onset REM episodes, immediately after wakefulness (2 naps) or after a short stage N1 (3 naps), and a very short mean sleep latency (1 minute 24 seconds; normal >8 minutes). Human leukocyte antigen typing was DQB1*0602, DQA1*0102, and DRB1*1501, and the CSF hypocretin-1 was undetectable, confirming the diagnosis of narcolepsy-cataplexy. A not previously tested archived CSF sample obtained when her serum was reported NMDAR antibody-positive elsewhere, and aliquots of another serum sample also considered positive, were comprehensively examined for immunoglobulin G antibodies to the GluN1 subunit of the NMDAR using brain immunohistochemistry, cultured live neurons, and cell-based assays, and all were negative.²

Discussion. Narcolepsy-cataplexy is a chronic disorder characterized by excessive daytime sleepiness and sudden loss of muscle tone triggered by emotions (cataplexy) caused by an irreversible loss of hypocretin-producing neurons.³ Pediatric narcolepsy-cataplexy is frequently unrecognized because cataplexy may be absent or subtle at onset, and occurs with a spectrum of motor symptoms that can range from negative (hypotonia) to active mood-dependent dyskinesias, including perioral dyskinetic or dystonic movements.⁴ These are in contrast with the complex and severe orofacial or limb dyskinesias of anti-NMDAR encephalitis that are not mood-related and usually occur in the acute stage of the disease when most patients have other deficits or decreased

Supplemental data
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Table Differential diagnosis between pediatric narcolepsy with cataplexy and anti-NMDAR encephalitis

	Narcolepsy with cataplexy	Anti-NMDAR encephalitis
Pathogenic mechanism	Irreversible loss of hypocretin-producing neurons of probable autoimmune etiology (target unrelated to NMDAR)	Antibody-mediated decrease of synaptic NMDAR
Risk factors and triggers	HLA DRB1*0602, DQA1*0102, and DRB1*1501; some cases triggered by a type of influenza vaccine (H1N1)	Age-/sex-dependent tumor association (ovarian teratoma); some cases triggered by herpes simplex encephalitis
Onset, course of the disease	Rapid onset, stabilization, and persistence of symptoms (chronic disease)	Rapid onset, frequent decrease of the level of consciousness, coma; slow but frequent recovery
Sleep disturbances	Daytime sleepiness (always); other symptoms: sleep paralysis, hypnagogic hallucinations, REM sleep behavior disorder	Insomnia (almost constant at disease onset); hypersomnia can occur during the phase of recovery (usually months after disease onset)
Abnormal movements	Cataplexy; it can be absent or subtle at symptom onset; may occur with a wide spectrum of movement disorders (typically mood-related)	Absence of cataplexy; movement disorders very frequent; predominant orofacial and limb dyskinesias (mood-independent); eventually resolve
Change in behavior	Frequent but milder than in anti-NMDAR encephalitis; cases with concurrent schizophrenia have been reported	Presentation with prominent psychiatric symptoms, psychosis, catatonia, mutism; during recovery: protracted behavioral, cognitive deficits
Cognitive deficits	Infrequent or absent	Memory deficits and executive dysfunction
Other symptoms	Absence of seizures; autonomic dysfunction: pupillary abnormalities, hypothermia, change in sympathetic and cardiovascular activities (milder than in anti-NMDAR encephalitis)	Frequent seizures or status epilepticus; frequent autonomic instability: tachycardia, bradycardia, fluctuation of blood pressure, hyperthermia, sialorrhea, hypoventilation
Weight gain	Frequent weight gain during the first months of the disease	Loss of weight during the first months of the disease (e.g., coma); several months after disease onset, while recovering, patients may develop hyperphagia (Kleine-Levin-like syndrome)
Ancillary tests	CSF usually normal	CSF mild pleocytosis in 90% of the patients; frequent oligoclonal bands
	EEG normal	EEG abnormal in >90% of cases
	MRI normal	MRI abnormalities in ~40%
Diagnosis	Polysomnography may show REM sleep latency ≤ 15 min; MSLT: mean latency ≤ 8 min and 2 or more sleep-onset REM periods, or CSF hypocretin ≤ 11.0 pg/mL	CSF immunoglobulin G antibodies to the GluN1 subunit of the NMDAR; serum antibodies frequently present
Treatment	Symptomatic therapy (e.g., methylphenidate, modafinil, ^a sodium oxybate ^a); the early use of immunotherapy has unclear effects	Immunosuppressive therapy (e.g., steroids, IV immunoglobulin, plasma exchange, rituximab, or cyclophosphamide)
Outcome	Chronic disorder	Substantial recovery in 80% of patients

Abbreviations: MSLT = multiple sleep latency test; NMDAR = NMDA receptor.

^a Off-label medication used in children according to European Medicines Agency and US Food and Drug Administration rules.

level of consciousness (table).⁵ Patients with anti-NMDAR encephalitis usually present with insomnia, not hypersomnia. If hypersomnia occurs, it is during the recovery phase, several months after symptom onset.⁶

In a cohort of patients with diverse symptoms tested for NMDAR antibodies using a live cell-based assay similar to that used initially in this patient, 23% of cases considered antibody-positive did not have anti-NMDAR encephalitis or autoimmune disorders (e.g., glioma and leukodystrophy, among others).⁷ In our patient, more specific and comprehensive immunologic testing including CSF and serum demonstrated that she did not have NMDAR antibodies.² This case emphasizes the difficulties in recognizing narcolepsy-cataplexy in children, the importance of prioritizing the clinical assessment over a serologic test especially when the symptoms do not fit with the test result, and the need for including CSF and comprehensive immunologic studies for NMDAR antibody determination.

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This Week's *Neurology*® Podcast

When a serum test overrides the clinical assessment (see p. 1379)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the March 31, 2015, issue of *Neurology*. In the second segment, Dr. John Mytinger talks with Dr. Josep Dalmau about his paper on when a serum test overrides the clinical assessment. Dr. James Addington then reads the e-Pearl of the week about lissencephaly. In the next part of the podcast, Dr. Michelle Johansen focuses her interview with Dr. Mitch Elkind on the topic of stroke in the setting of systemic infection.

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