Narcolepsy Caused by Acute Disseminated Encephalomyelitis

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**Background:** Narcolepsy with cataplexy is caused by a selective loss of hypocretin-producing neurons, but narcolepsy can also result from hypothalamic and rostral brainstem lesions.

**Patient:** We describe a 38-year-old woman with severe daytime sleepiness, internuclear ophthalmoplegia, and bilateral delayed visual evoked potentials. Her multiple sleep latency test results demonstrated short sleep latencies and 4 sleep-onset rapid eye movement sleep periods, and her cerebrospinal fluid contained a low concentration of hypocretin. Magnetic resonance imaging showed T2 and fluid-attenuated inversion recovery hyperintensity along the walls of the third ventricle and aqueduct, which are consistent with acute disseminated encephalomyelitis.

**Results:** After treatment with steroids, this patient’s subjective sleepiness, hypersomnia, and hypocretin deficiency partially improved.

**Conclusions:** Autoimmune diseases such as acute disseminated encephalomyelitis can produce narcolepsy. Most likely, this narcolepsy is a consequence of demyelination and dysfunction of hypocretin pathways, but direct injury to the hypocretin neurons may also occur.

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**REPORT OF A CASE**

A previously healthy, 38-year-old, black, South African woman was admitted to Ga-Rankuwa Hospital, Pretoria, Republic of South Africa, with 6 weeks of severe daytime sleepiness and hypersomnia (total sleep time about 16 of every 24 h). She reported forgetfulness and impaired vision but denied cataplexy, sleep paralysis, hypnagogic hallucinations, a preceding viral infection, fever, rash, or vaccination. Her body mass index was increased at 32.3 kg/m². She was disoriented to time and place, and she was inattentive and had impaired memory. Visual acuity was 20/300 OD and 20/150 OS, and the pupils were 4 mm, with a weak reaction to light. She had bilateral internuclear ophthalmoplegia with poor up-gaze and convergence. Cerebrospinal fluid had no white blood cells, a normal glucose level, 44 mg/dL protein, and a normal IgG index. Her morning cortisol level was 8 µg/dL. (221 nmol/L; normal range, 9.2-22 µg/dL [248-607 nmol/L]).

Electroencephalography performed while the patient was awake showed frontal intermittent delta activity, a slow al-
pha rhythm, and excessive theta activity. Magnetic resonance imaging revealed multiple areas of T2 and fluid-attenuated inversion recovery hyperintensity involving the corona radiata and deep periventricular gray matter. This region of increased signal intensity was especially prominent around the third ventricle and aqueduct, involving most of the hypothalamus (Figure) and extending rostrally to the basal forebrain. Scattered regions of contrast enhancement were evident throughout the hypothalamus, especially near the fornix. Rapid plasma reagin, serum angiotensin-converting enzyme, human immunodeficiency virus antibodies, autoantibody panel, and liver and thyroid function test results were all normal. She was positive for human leukocyte antigens DR2 and DQB1*0602. The unextracted hypocretin-1 level in CSF was low (87 pg/mL [24.4 pmol/L]; normal, >200 pg/mL [56.1 pmol/L]).

On the basis of these laboratory results and her monophasic onset of symptoms, ADEM was diagnosed, and the patient was treated with high-dose steroids. Magnetic resonance imaging 1 month later showed smaller, fewer lesions.

Six months after her initial examination, the patient’s subjective sleepiness was partially improved, but she still took 3 to 4 nonrefreshing naps per day, each lasting as long as an hour. Although she continued to have mildly impaired memory and visual acuity, with slight slowing of visual evoked potentials, her extraocular movements and attention were normal. Her multiple sleep latency test results demonstrated an average sleep latency of 4.4 minutes and SOREM periods in all 4 naps. The CSF hypocretin-1 level (148 pg/mL [41.5 pmol/L]) had increased to the intermediate range.1 On the basis of these test results and her persistent sleepiness, narcolepsy without cataplexy was diagnosed. The patient’s sleepiness partially responded to methylphenidate hydrochloride.

One year after her initial examination, some sleepiness persisted, with a total daily sleep time of 12 hours without methylphenidate hydrochloride. Overnight polysomnography results showed 7.6 hours of sleep with a sleep efficiency of 95%, REM latency of 52 minutes, 20% stage 1 sleep, normal proportions of all other stages, and no sleep-disordered breathing. The multiple sleep latency test results were essentially unchanged, with an average sleep latency of 2.6 minutes and SOREM periods in 4 of 5 naps.

Peptides are most stable when frozen, but samples could be maintained only at ambient temperature during the 9 days of shipping from the Republic of South Africa to the United States. Therefore, CSF also was analyzed from 3 patients with other neurologic diseases (2 with motor neuron disease and 1 with spastic dysphonia). These specimens were collected within a few weeks of our patient’s first lumbar puncture and shipped together with this first sample. Hypocretin levels for the control subjects were all in the normal range (241-290 pg/mL [67.6-81.4 pmol/L]).

We describe a patient with narcolepsy and low hypocretin levels due to ADEM. Although most patients with ADEM have CSF lymphocytosis, a few may have no ex-
state-regulatory, hypocretin-responsive areas in the midbrain and pons such as the raphe nuclei. In addition, her sleepiness was coincident with her ADEM. Thus, we think it is most likely that ADEM caused her narcolepsy, especially because her hypocretin level and subjective sleepiness partially improved after treatment with steroids.

Unlike previous patients with hypersomnia due to ADEM, our patient had SOREM periods, possibly because she is DQB1*0602 positive, and these individuals enter REM sleep more quickly. More likely, it is because her lesions involved REM-regulating pathways. The hypocretin neurons probably suppress REM sleep by increasing the activity of the locus coeruleus and dorsal raphe neurons via projections through the periaqueductal gray and midbrain tectum. Impaired hypocretin signaling along these pathways probably contributed to our patient’s SOREM periods.

Low levels of hypocretin are specific for narcolepsy with cataplexy but have also been described in a few patients with secondary narcolepsy. In 2, the hypocretin deficiency occurred after removal of a dienecphalic tumor. In 2 others, narcolepsy was part of a hypothalamic syndrome associated with neural degeneration or central hypoventilation. However, not all patients with secondary narcolepsy are hypocretin deficient, and the sleepiness and cataplexy of some may be caused by focal lesions of hypocretin targets.

Our patient’s hypersomnia, or increase in total sleep during 24 hours, was probably not caused by hypocretin deficiency alone. Patients with idiopathic narcolepsy and mice lacking hypocretin-producing neurons have normal daily amounts of sleep. In contrast, most patients with secondary narcolepsy due to hypothalamic injury have hypersomnia. Nonecselective lesions of the lateral hypothalamus in rats and monkeys also produce hypersomnia, most likely reflecting the loss of other wake-promoting neurons such as the histaminergic neurons of the tuberomamillary nucleus. An improved understanding of these other wake-promoting systems may shed light on the many causes of sleepiness.

This patient demonstrates that narcolepsy can result from an autoimmune process. The main cause in ADEM is probably demyelination and dysfunction of hypocretin pathways, but direct injury to the hypocretin neurons may also occur.

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