A 69-year-old man with anti-Ma2 paraneoplastic encephalitis presented with subacute onset of severe hypersomnia, memory loss, parkinsonism, and gaze palsy. A brain magnetic resonance imaging study showed bilateral damage in the dorsolateral midbrain, amygdala, and paramedian thalami. Videopolysomnography disclosed rapid eye movement (REM) sleep behavior disorder, and a Multiple Sleep Latency Test showed a mean sleep latency of 7 minutes and 4 sleep-onset REM periods. The level of hypocretin-1 in the cerebrospinal fluid was low (49 pg/mL). This observation illustrates that REM sleep behavior disorder and narcoleptic features are 2 REM-sleep abnormalities that (1) may share the same autoimmune-mediated origin affecting the brainstem, limbic, and diencephalic structures and (2) may occur in the setting of the paraneoplastic anti–Ma2-associated encephalitis.

**Keywords:** REM sleep behavior disorder, narcolepsy, hypocretin-1, anti–Ma2-associated encephalitis

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Figure 1—Axial FLAIR brain magnetic resonance imaging study (MRI) shows bilateral hyperintensities in the amygdala (white arrows) and dorsolateral midbrain (grey arrow) (A), and polysomnography demonstrates characteristic features of rapid eye movement (REM) sleep behavior disorder (sustained tonic electromyogram (EMG) activity in the chin and excessive phasic EMG activity in the lower limbs channels during REM sleep) (B).

DISCUSSION

To the best of our knowledge, this is the first documented case of anti-Ma2 encephalitis associated with both secondary RBD and narcolepsy. This observation indicates that abnormal manifestations of REM sleep, such as REM sleep without atonia and REM sleep intrusion into wakefulness, may share a common autoimmune-mediated origin. It should be noted that idiopathic narcolepsy is a condition thought to be mediated by autoimmune mechanisms; where clinical symptoms suggestive of RBD occur in up to 36% of the patients. RBD and idiopathic narcolepsy are 2 disorders characterized by obscure sleep-wake boundaries. In RBD, components of 1 state (sustained muscle contraction characteristic of wake) appear in another state (REM sleep), leading to dream-enacting behaviors. In narcolepsy, components of REM sleep (muscle atonia and vivid dreams) intrude into wakefulness, manifesting as episodes of cataplexy, sleep paralysis, and hypnagogic hallucinations.

Anti-Ma2-associated encephalitis is a paraneoplastic condition characterized by upper brainstem, limbic system, and hypothalamic impairment. The encephalitis process reflects an abnormal autoimmune-mediated response against the Ma2 protein, which is expressed in all neurons of human brain, particularly in the brainstem, hippocampus, amygdala, and diencephalic structures, including the hypothalamus and thalamus. In these areas, pathology studies demonstrate inflammatory infiltrates, neuronal loss, and gliosis. Neurologic symptoms usually precede detection of a testicular germ-cell or non-small cell lung cancer, but, in some subjects, no underlying neoplasm is ever identified. Clinical presentation depends on the area of the brain that is affected. In our patient, vertical gaze palsy and atypical parkinsonism were attributable to midbrain pathology, whereas short memory loss, episodes of fear, and personality changes were probably mediated by limbic-system involvement. We speculate that, in our patient, RBD and the narcoleptic features were also secondary to brain damage linked to the inflammatory process.

RBD is a parasomnia characterized by lack of muscle atonia during REM sleep. RBD frequently occurs in the setting of neurodegenerative diseases. It also has been described as being associated with autoimmune disorders, such as potassium-channel antibody-associated limbic encephalitis. RBD has not been reported in subjects with autoimmune paraneoplastic disorders, such as anti-Ma2-associated encephalitis. The pathophysiology of RBD lies in a dysfunction of the brainstem structures that regulate REM-sleep muscle tone (e.g., subcoeruleus nucleus) and their anatomic connections, including those with the amygdala. Bilateral lesions of the dorsolateral mesopontine tegmentum of laboratory animals produce REM sleep without atonia. Alternatively, RBD may occur in disorders associated with direct damage of the limbic system and no apparent primary brainstem impairment. It has been speculated that limbic-system dysfunction contributes to the development of the characteristic frightening dreams and the violent nature of the sleep behaviors displayed by patients with RBD. In our case, the presence of RBD was likely due to primary impairment of the REM sleep-related structures within the dorsolateral midbrain tegmentum and amygdala.

Idiopathic narcolepsy is characterized by selective loss of hypocretin-producing neurons in the posterior hypothalamus. Hypocretin is a neuropeptide of hypothalamic origin that promotes wakefulness and inhibits REM sleep. Thus, impairment of

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the hypocretin system results in inappropriate intrusion of REM sleep, leading to episodes of sleepiness and cataplexy. In idiopathic narcolepsy, an autoimmune basis is suspected because of the strong association between narcolepsy and the HLA DQB1*0602 allele. Secondary narcolepsy occurs in focal lesions in the hypothalamus resulting in decreased hypocretin production. Hypersomnia has been noted to occur in up to 32% of the subjects with anti–Ma2-associated encephalitis, but cataplexy has been reported in fewer than 3%. Low or undetectable hypocretin-1 levels in the cerebrospinal fluid have been reported in 6 patients with anti–Ma2-associated encephalitis and hypersomnia in whom cataplexy was not documented. Sleep studies have been performed in only 1 subject with anti–Ma2-associated encephalitis plus hypersomnia, showing, as in our case, reduced sleep efficiency on nocturnal polysomnography and decreased mean sleep latency and sleep-onset REM periods on the Multiple Sleep Latency Test. That patient had cataplexy but the hypocretin-1 level in the cerebrospinal fluid was not measured. In our patient, anti–Ma2-associated encephalitis was associated with hypersomnia, sleep-onset REM periods on the Multiple Sleep Latency Test, and a low concentration of hypocretin-1 in the cerebrospinal fluid. Thus, it can be speculated that these narcoleptic features were likely caused by the abnormal autoimmune response directed against the hypothalamic hypocretin-synthesizing neurons. The finding that our patient was HLA DQB1*0602 negative suggests that this particular HLA allele was not required for some narcoleptic features to develop in anti–Ma2-associated encephalitis.

REFERENCES