Hypersomnia and Low CSF Hypocretin-1 (Orexin-A) Concentration in a Patient with Multiple Sclerosis Showing Bilateral Hypothalamic Lesions

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Abstract

A 45-year-old Japanese woman with multiple sclerosis (MS) manifested hypersomnia in a relapse of MS. Magnetic resonance imaging revealed new bilateral hypothalamic lesions, and the hypocretin-1 level in the cerebrospinal fluid (CSF) was significantly low. Methylprednisolone pulse treatment successfully resolved the hypersomnia and the left hypothalamic lesion, and it normalized the hypocretin-1 level in the CSF. These findings suggest that the hypothalamic hypocretin (orexin) system may be crucial to maintaining the arousal level and that lesions in the system can cause hypersomnia in MS.

Key words: multiple sclerosis, hypersomnia, hypocretin, orexin, hypothalamus

Introduction

Hypocretin (also known as orexin) is a newly discovered hypothalamic neuropeptide (1, 2), whose function is relevant to the arousal stimulating system (3). Previous studies have revealed that the hypocretin-1 (orexin-A) level in cerebrospinal fluid (CSF) is decreased in narcolepsy (4) and in a few other conditions showing hypersomnia, such as diencephalic stroke (5) and post resection of tumor in the hypothalamus (6). Although hypersomnia is a rare complication in multiple sclerosis (MS) (7), the prevalence of sleep attack is significantly high in comparison with normal subjects (8). We present a patient with MS, who developed hypersomnia accompanied by bilateral hypothalamic lesions and a decreased CSF hypocretin-1 concentration. After corticosteroid treatment, she recovered from the hypersomnia, the left hypothalamic lesion disappeared, and the CSF hypocretin-1 level returned to normal. This is the first case of MS with hypothalamic lesions, suggesting a causal relationship between hypersomnia and decreased CSF hypocretin-1 level.

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Case Report

A 45-year-old Japanese woman was admitted to the hospital because of hypersomnia. At age 41, she developed one-and-a-half syndrome with right gaze palsy. Total protein in CSF was 35 mg/dl (normal range: less than 40 mg/dl), and myelin basic protein (MBP) in CSF was 7.5 ng/ml (normal range: less than 4.0 ng/ml). Brain magnetic resonance image (MRI) revealed T2-high lesions in the dorsal pons and midbrain (Figs. 1A, B). A diagnosis of probable MS was made, and methylprednisolone (M-PSL) pulse combined with intravenous immunoglobulin administration (IVIG) and immunoadsorption (IA) improved the symptoms. At age 43, she developed weakness of the right upper limb. Cervical MRI revealed new T2-high lesions in the cervical spinal cord (Fig. 1C). A diagnosis of definite MS was made on the basis of disseminations both in time and space (9). M-PSL pulse combined with IVIG and IA achieved remission. Two months before admission, MRI revealed a new lesion in the right hypothalamus (Fig. 2A), but no neurological symptoms were noted. Forty-five days before admission, the patient suffered from hypersomnia; she would suddenly fall asleep during a conversation and while cooking.

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Neurological examination on admission showed hypersomnia and mild sequelae of the previous MS attacks, including ophthalmoplegia, weakness of the right upper limb and urinary incontinence. Her mentation was normal during wakeful periods, but she suddenly fell asleep during physical examination. Neither calling her name loudly nor vigorously shaking her by the shoulders awakened her. She was awake only intermittently; she slept almost all day. MRI presented a new T2-high and FLAIR-high lesion of the left hypothalamus (Fig. 2B), adding to the old right lesions. As a result, bilateral hypothalamic lesions were observed at the time. No other new lesions were detected. The basic rhythm on electroencephalogram (EEG) showed slow diffuse alpha waves (8 Hz) and high-amplitude delta waves (1–2 Hz) in the frontal areas. Paradoxical alpha blocking was not detected. Nocturnal polysomnography did not reveal the presence of sleep apnea syndrome. CSF examination on admission revealed that protein content was moderately elevated at 63 mg/dl (normal range: less than 40 mg/dl). Pleocytosis and oligoclonal IgG band were not detected. MBP was 0.5 ng/ml (normal range: less than 4.0 ng/ml). Culture and cytology of CSF presented no abnormalities. Hypocretin-1 level in CSF was measured using radioimmunoassay kits (Phoenix Pharmaceuticals, Belmont, CA, USA) (4). Hypocretin-1 level in CSF was below 40 pg/ml (normal range: 291±130, mean±2SD) (10). Laboratory and physical examination did not show any findings which suggested collagen diseases, such as Behçet disease and sarcoidosis.

A diagnosis of MS relapse in the left hypothalamic area was made, and M-PSL pulse treatment (1 g per day, for three days), followed by oral 30 mg of PSL per day, was administered from the 4th hospital day. PSL was tapered off by 5 mg every 4 days. Three days after the start of M-PSL pulse, the patient’s hypersomnia was resolved completely. Twenty days after the start of M-PSL pulse, CSF protein content was normalized: 33 mg/dl. Hypocretin-1 level in CSF was 167 pg/ml. EEG finding showed normal alpha rhythm (10 Hz) and a trace of delta waves. Twenty-eight days after the start of M-PSL pulse, MRI revealed the disappearance of the left hypothalamic lesion.
hypothalamic lesion (Fig. 2C), but the right hypothalamic lesion remained.

Discussion

On admission, our patient presented with a hypersomnolent state, but she did not have clinical signs of narcolepsy or paradoxical alpha blocking in EEG. The hypersomnolent state in our patient was considered a consciousness disturbance, resulting from dysfunction of the ascending arousal reticular system, rather than a disturbance of the switching system between wakefulness and sleep, as in narcolepsy.

The optic chiasm, brainstem, cerebellum and spinal cord are commonly involved in MS (7). Although the hypothalamus is abundant in grey matter and it seems to be spared in MS, pathological investigation has demonstrated that almost all MS patients have hypothalamic demyelinated lesions, and 18% of MS patients have hypercellular lesions in the hypothalamic grey matter (11). In addition, the left hypothalamic lesion in our patient was M-PSL pulse responsive. According to these findings, the hypothalamic lesions of our patient were assumed to be demyelinated and inflammatory lesions caused by MS.

It has been demonstrated that hypothalamic hypocretin-containing neurons project to and stimulate the ascending arousal reticular system, which includes the Raphe nucleus, locus ceruleus and tuberomammillary nucleus (3). Hypocretin has been indicated to be a key peptide in an awakening system. This indication was confirmed by recent reports demonstrating that orexin knockout mice (12) and dogs with disruption of the hypocretin receptor 2 gene (13) exhibited human narcolepsy-like phenotype. It is, therefore, suggested that MS lesions in the hypothalamic areas decreased CSF hypocretin-1 level and caused hypersomnia in our patient. It is interesting that the hypersomnia did not appear until the hypothalamic areas were bilaterally involved and that the CSF hypocretin-1 level returned to normal after remission of the unilateral hypothalamic lesion in our patient. These findings suggest that the hypothalamic system on one side can maintain wakefulness and CSF hypocretin-1 level.

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References