□ CASE REPORT □

Possible Mechanism of Secondary Narcolepsy with a Long Sleep Time Following Surgery for Craniopharyngioma

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Abstract

A 19-year-old woman suffered from severe excessive daytime sleepiness accompanied with long sleep episodes both in the daytime and nighttime and frequent episodes of cataplexy shortly after the removal of craniopharyngioma in the intrasellar space. Multiple sleep latency test showed a typical finding of narcolepsy, and cerebrospinal fluid orexin concentration was below the narcolepsy cut-off value. MRI-tractography showed a clear lack of neuronal fiber connections from the hypothalamus to the frontal lobe. SPECT using ¹²³I-IMP showed frontal hypoperfusion. These connection damages could have been responsible for the occurrence of narcolepsy-like symptoms and long daytime sleep episodes in this case.

Key words: craniopharyngioma, secondary narcolepsy, orexin, MRI-tractography, SPECT

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Introduction

Narcolepsy is a disorder characterized by excessive daytime sleepiness (EDS) and REM sleep-related symptoms including cataplexy, hypnagogic hallucinations and sleep paralysis. Orexin (hypocretin) is well known as a hypothalamic peptide which has an important role in maintaining wakefulness, and it has been reported that destruction of the hypocretin (orexin) receptor 2 gene is responsible for the occurrence of canine narcolepsy (1). Orexin knockout mice have also been reported to show narcoleptic symptoms (2). As for humans, Mignot et al reported that more than 90% of narcoleptic patients with cataplexy show abnormally low CSF-orexin levels (3). These studies indicate that dysfunction of the orexinergic system plays an important role in the pathogenesis of narcoleptic patients with cataplexy. Muller et al reported that 4 out of 115 childhood craniopharyngioma patients were diagnosed as narcolepsy (4). Tachibana et al reported that craniopharyngioma patients after surgery were diagnosed as narcolepsy (5). Several cases have been reported to have hypothalamic lesions, especially craniopharyngiomas showing narcolepsy-like symptoms, together with nocturnal long sleep episodes. (5, 6) These cases have been operationally classified into the category of “secondary/symptomatic narcolepsy which occurs clearly based on medical or neurological disorder” (International Classification of Sleep Disorders-2: ICSD-2) (7). However, the detailed mechanisms of these characteristic symptoms in patients with craniopharyngioma have not yet been clarified.

We encountered a patient showing cataplexy and long sleep episodes during both the daytime and nighttime following resection of craniopharyngioma. From both the laboratory data and neuroimaging results, including single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and MRI-tractography, we attempted to further understand the mechanisms of the narcoleptic symptoms and extremely long sleep episodes in this case.

Case Report

A woman with a chief complaint of headache, which had lasted for about 1 year, was given a diagnosis of craniopharyngioma.

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Figure 1. Left panel (before surgery): A tumor (arrow) 30 mm in maximum dimension in the intrasellar area. Right panel (after surgery): The expansion of the third ventricle and atrophy of the pituitary gland, as well as a cavity forming in the hypothalamic area after surgery.

Figure 2. Marked shortening of sleep latency, and sleep onset REM period as well as frequent episodes of REM sleep were observed.

ryngioma at 19 years of age. At that time, head MRI revealed a capsuled tumor 30 mm in maximum dimension compressing the surrounding tissues in the intrasellar space (Fig. 1, left). Shortly after the diagnosis, she underwent transnasal resection of the craniopharyngioma. Within 1 week after surgery, she developed diabetes insipidus and panhypopituitarism. She also presented with short term memory deficit, left hemiparesis and left lateral visual field defect. At the same time, she started to suffer from EDS lasting throughout the day, and cataplexy with sudden loss of knee strength triggered by laughter or surprise once or twice each day. She slept for more than 10 hours at night and took frequent naps in the daytime with durations of 1 to 4 hours. Polysomnographic (PSG) findings revealed that total sleep time was relatively long (517 min), REM latency was short (3.5 min), percentage of REM stage sleep as a percentage per total sleep time was remarkably high (38.1%) and the appearance of REM stage was remarkably frequent (Fig. 2). She did not have sleep apnea syndrome (apnea hypopnea index = 0/hr). On multiple sleep latency test (MSLT), mean sleep latency was 1.0 min and sleep onset REM periods (SOREMPs) were observed for 4 times/4 sessions. However, neither sleep paralysis nor hypnagogic hallucinations were reported by the patient. Judging from the existence of typical cataplexy and the results of MSLT, the patient was given a diagnosis of secondary narcolepsy. For the treatment of EDS, she was prescribed modafinil (300

mg/day) orally. However, as shown in Fig. 3, severe EDS accompanying long sleep episodes during both the daytime and nighttime was not improved. At that time, she appeared apathetic, and complained that she did not feel like doing anything because of unbearable daytime sleepiness.

She visited the outpatient clinic of the Japan Somnology Center at age 22 for treatment of EDS. She had no history of other neurologic, psychiatric or sleep disorders, or a family history of sleep disorders. Her body characteristics appeared normal (height: 157 cm, weight: 50 kg, BMI: 20.3), and she reported that her body weight had not changed after surgery. HLA typing showed the presence of DRB1*0101/0901-DQB1*0303/0501. Orexin concentration in her cerebrospinal fluid was measured using radioimmunoassay kits (Phoenix Pharmaceuticals, Belmont, CA, USA) and the value was 70.8 pg/ml (normal: over 200 pg/ml; cutoff value for narcolepsy: 110 pg/ml). MRI revealed expansion of the 3rd ventricle, and atrophy of the pituitary gland as well as a cavity forming in the whole hypothalamus (Fig. 1, right). MRI-tractography imaging was obtained using the Diffusion Tensor Visualizer (dTV—free software program provided by the University of Tokyo Hospital (<http://www.ut-radiology.umin.jp/people/masutani/dTV.htm>), and the findings showed a lack of neuronal fibers connecting hypothalamus to frontal lobe (Fig. 4). SPECT with ^{123}I -IMP showed slightly lowered perfusion in the whole area and marked hypoperfusion in the frontal area (Fig. 5).

Figure 3. She slept for about over 10 hours during the night and took naps for 1 to 3 hours in the daytime even under medication with modafinil. After adding methylphenidate (20 mg/day), EDS symptoms improved.

Figure 4. Left panel: Tractographic image of the patient. A lack of neuronal fiber connections between the hypothalamus and the frontal lobe can be seen. Right panel: Image of a normal control, a 20-year-old woman.

Figure 5. Left panel: Sagittal view. Right panel: Horizontal view. Hypoperfusion was found in the frontal lobe (dotted circle).

Considering that 300 mg dose of modafinil was insufficient for the treatment of the patient's sleepiness, methylphenidate (20 mg/day) was added to the previously-prescribed dose of modafinil. After that, EDS symptoms improved to a level at which she could follow basic daily routines such as rehabilitation and taking a walk. For treatment of her cataplexy, 20 mg/day of clomipramine was adminis-

tered, and symptom frequency decreased remarkably to about less than once a week.

Discussion

This case showed clinical features of typical of narcolepsy (i.e. typical cataplexy clearly triggered by emotion, and the

frequent appearance of SOREMP on MSLT) and extremely long sleep episodes during both the nighttime and daytime. Although remarkable long sleep episodes are not frequently observed in narcolepsy cases except for atypical cases (narcolepsy with long sleep time) (8), this case met the ICSD-2 criteria of secondary narcolepsy (6).

Judging from the clinical course, the expansion and/or excision of the craniopharyngioma was thought to play a definitive causative role for the occurrence of these symptoms. Muller et al reported that 4 out of 115 childhood craniopharyngioma patients were diagnosed as narcolepsy before undergoing surgery for the treatment of the disorder (16). However, considering that the patient complained of only headache before the surgery, the characteristic EDS symptoms of this patient were thought to have developed after the surgery. Given this, the present case could be compatible with the case reported by Tachibana et al in that severe EDS became apparent after the surgery for craniopharyngioma (5). For these cases, the resection of the tumor seemed to have a larger influence than the mass effect of tumor itself.

This case was not positive for HLA-DRB1*1501/DQB1*0602, a well known marker of Japanese narcolepsy with cataplexy patients (9), probably because of secondary pathology to craniopharyngioma. These clinical features (frequent episodes of REM sleep on MSLT and long sleep time during both day and night) are quite similar to those reported by Tachibana et al (5). Taking the present case and their report together, it could be possible that cases with craniopharyngioma are sometimes complicated by both narcolepsy-like symptoms and long sleep episodes throughout the day.

Similar to the previously reported cases with secondary narcolepsy due to craniopharyngioma (5), the CSF orexin concentration in this case was shown to be below the cut-off level for narcolepsy (3). Orexin neurons localized in the lateral hypothalamus (LHA) have widespread projection to the brain stem, basal forebrain, cortex and spinal cord, and are known to be important in the control of sleep-wakefulness, autonomic regulation, neuroendocrine homeostasis and appetite (10). It is known that lowered CSF orexin levels are frequently observed in patients with narcolepsy-cataplexy (3), and this finding is reported to be related to both the occurrence of cataplexy (11) and increased REM propensity (12) of the disorder. Judging from the above-indicated MRI findings, damage to orexin neurons in the hypothalamus due to the expansion and/or excision of craniopharyngioma could be responsible for the lowered secretion of CSF orexin, resulting in the above narcoleptic symptoms. (5, 10)

To the best of our knowledge, this is the first study to perform MRI tractography on a patient with secondary narcolepsy. The result revealed a clear lack of neuronal connections between the hypothalamus and the frontal lobe. This finding could correspond to the hypofrontality of perfusion which was observed on SPECT with ¹²³I-IMP findings. These findings are similar to those in our previously re-

ported case with post-traumatic hypersomnia (13). Interestingly, both of these cases showed long sleep episodes during both the daytime and nighttime. The wakefulness-generating neurons including not only orexinergic and histaminergic neurons but also noradrenergic, dopaminergic and serotonergic neurons have also been reported to project from the hypothalamus to the frontal area (14-16). Considering this, a lack of neuronal connections from the hypothalamus to the frontal lobe might have contributed to the occurrence of the above-indicated long sleep episodes all through the day in the current case.

In conclusion, we speculated that damage to hypothalamic orexin neurons, together with a lack of connections from the hypothalamus to the frontal lobe, were responsible for the occurrence of characteristic symptoms in this case. This case may provide clues for clarifying the mechanisms of narcolepsy with a long sleep time, or idiopathic hypersomnia with a long sleep time (8) in association with the hypothalamic-frontal lobe connection.

The authors state that they have no Conflict of Interest (COI).

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