Decreased Cerebrospinal Fluid Hypocretin-1 Levels Near the Onset of Narcolepsy in 2 Prepubertal Children

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Abstract: We present 2 cases of narcolepsy with prepubertal onset. Although excessive daytime sleepiness and cataplexy had appeared early in both patients, the presence of sleep-onset rapid eye movement periods was detected several months after the onset of hypersomnia. The levels of hypocretin in the cerebrospinal fluid were reduced when measured 3 weeks (Patient 1) and 2 months (Patient 2) after the appearance of hypersomnia, before the presence of sleep-onset rapid eye movement periods was confirmed. Because the symptoms of narcolepsy in children are often obscure and easily mistaken as other diseases, and the electrophysiologic studies may not be specific in the early stage, the definite diagnosis tends to be delayed. Measurement of hypocretin-1 levels in the cerebrospinal fluid is useful for the early diagnosis of narcolepsy with prepubertal onset.

Key Words: narcolepsy, prepubertal onset, hypocretin, multiple sleep latency test

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INTRODUCTION

NARCOLEPSY IS CHARACTERIZED BY EXCESSIVE DAYTIME SLEEPINESS AND CATAPLEXY, OFTEN ACCOMPANYED BY SLEEP PARALYSIS AND HYPNAGOGIC HALLUCINATIONS. Although the mechanism of this disease remains unknown, recent studies have demonstrated the neuropeptides hypocretins exclusively in the dorsolateral hypothalamus. Subsequent research on these neuropeptides has indicated that hypocretins control the sleep-wake state and that human narcolepsy is a hypocretin deficiency syndrome in most patients.1 The onset of narcolepsy is gradual and usually between 15 and 35 years of age,2 and the incidence of prepubertal onset is very low. A large prospective series identified only 5% of the cases as prepubertal.3 We present 2 cases of narcolepsy with prepubertal onset, which showed decreased levels of hypocretin-1 in the cerebrospinal fluid (CSF) before the presence of sleep-onset rapid eye movement periods (SOREMPs) was confirmed.

CASE REPORTS

Case 1

A 7-year-old girl presented with unusual sleepiness and knee weakness. This previously healthy girl had suddenly started to take a nap everyday, although she rarely did so before. She frequently felt weak when she laughed and sat down suddenly due to weakness in the knees everyday. Excessive daytime sleepiness appeared 2 weeks before. Since then, she tended to drop things repeatedly. She rose during nocturnal sleep and felt frightened in the hypnagogic state. She had no history of sleep paralysis. Her family history and past history were unremarkable. Physical examination and neurologic examination disclosed no abnormalities except slowness of motion and speech. Routine blood and urine examinations were normal. The HLA typing was positive for DR2/DQw1. Since the possibility of degenerative diseases and central nervous system diseases including encephalitis were not completely excluded, CSF analysis was performed and revealed a white blood cell count of 3/mm3, a protein level of 14 mg/dL, and an IgG index of 0.38. Magnetic resonance imaging (MRI) showed an area of abnormally high signal intensity on T2-weighted images located in the amygdala of the right side (Figure 1). Although the first nocturnal polysomnogram (PSG) showed no SOREMPs and no apnea, a PSG performed 4 months later demonstrated 1 SOREM. A multiple sleep latency test (MSLT) conducted after the first PSG showed a mean sleep latency time of 6.5 minutes and no SOREMPs. Hence narcolepsy was diagnosed. Although treatment with methylphenidate hydrochloride (5 mg twice a day) and clomipramine hydrochloride (15 mg once a day) was initiated, it was not fully effective. Consequently, she needed to take naps and had cataplectic attacks, especially when she laughed. As the high signal intensity area in the amygdala gradually increased in size, surgical resection of the right amygdala was performed at the age of 13. However, the symptoms of narcolepsy did not improve. Pathologic examination of the resected specimen revealed a ganglioma. A 125I hypocretin-1 radioimmunoassay kit (Phoenix Pharmaceuticals, Belmont, CA) was used to measure the hypocretin-1 level in the CSF sample obtained 3 weeks after symptom onset, which had been stored at -80ºC for 10 years. The intrasay variability of the assay was 4.3% and the detection limit was 40 pg/mL, as determined in our department. The hypocretin-1 level in the CSF sample was 79 pg/mL, which was reduced compared to the reported values for age-matched control subjects (316±61 pg/mL for patients aged 5 to 9 years).4

Case 2

A 10-year-old girl presented with excessive daytime sleepiness beginning 1 week after she bruised her head while playing in a volleyball game. In spite of long hours of nocturnal sleep, she had problems keeping awake during classes and was found to fall asleep in the hallway. A few weeks after the onset of excessive daytime sleepiness, she started to experience sudden weakness in her neck and knees when she was laughing or exercising and often had difficulties maintaining a standing posture several times a day. Cataplexy was diagnosed. Moreover, she woke at least once during nocturnal sleep. She had no history of hypnagogic
hallucination and sleep paralysis. Her homeroom teacher noticed her abnormal behaviors and prompted her to visit our hospital. Her family history and past history were unremarkable. Although she fell asleep in the waiting room, her sleepiness improved during the examination. Physical examination and neurologic examination showed no abnormalities. The results of routine blood and urine tests were normal. Tests for antibodies against Japanese B encephalitis virus, measles, rubella, varicella-zoster virus, and cytomegalovirus ruled out recent infection by these agents. The HLA typing was positive for DR2. Since a possibility of central nervous system disease could not be excluded, CSF analysis was performed and revealed a white blood cell count of 4/mm$^3$ and a protein level of 21 mg/dL. Electroencephalograms and MRI were normal. The initial nocturnal PSG revealed a sleep latency of 2 minutes, no SOREMPs, and no apnic episode. While the first MSLT showed a mean sleep latency time of 2.5 minutes and no SOREMPs, an MSLT conducted 6 months later revealed a mean sleep latency of time of 1 minute and 3 SOREMPs. Therefore narcolepsy was diagnosed. She was treated with methylphenidate hydrochloride (10 mg twice a day) and clomipramine hydrochloride (20 mg once a day), which partially improved both excessive daytime sleepiness and cataplexy. Fortunately her homeroom teacher fully understood her illness and supported her in her school life. Hypocretin-1 level in the CSF was measured once, 2 months after symptom onset, and the level was below the detection limit of 40 pg/mL (the values of age-matched control subjects were 309±46 pg/mL in patients 10 to 14 years old).4

This study was approved by the local ethics committee, and either the subjects or their families gave informed consent for the hypocretin measurement.

DISCUSSIONS

The hypocretins (orexins) are newly discovered neuropeptides derived from the same precursor gene and are synthesized by neurons exclusively located in the lateral, posterior, and perifornical hypothalamus.5 After animal studies demonstrated that genetic alteration in either hypocretin ligands or hypocretin receptor-2 cause narcolepsy in mice and dogs, many aspects of the circuitry of the hypocretin system have been identified. Consequently, the dominant activities of the hypocretin system have been proved to be maintenance of the waking state and suppression of REM entry.8 Human studies of hypocretin contents in tissues showed that CSF hypocretin-1 levels were undetectable (<40 pg/mL) in 7 of 9 patients with narcolepsy.9 Subsequently, a comprehensive study showed that 106 of 113 patients with International Classification of Sleep Disorders-defined narcolepsy and other disorders, including 3 with secondary hypersomnia/narcolepsy and 4 with another neurologic disorder, had CSF hypocretin-1 levels of 110 pg/mL or less.10 However, for patients with low CSF hypocretin-1 levels, a careful evaluation of clinical symptoms and neuroradiologic data could distinguish narcolepsy with cataplexy from other disorders. The sensitivity-specificity of low hypocretin-1 levels in patients with typical cataplexy has been indicated as extremely high.10 The diagnostic utility of CSF hypocretin-1 levels in patients with narcolepsy and cataplexy has been established.

In the present 2 prepubertal cases, decreased levels of CSF hypocretin-1 were detected, as is found in narcolepsy with adolescent or later onset. Therefore, measurement of CSF hypocretin-1 level would also be useful in the diagnosis of narcolepsy with precocious onset, even at a considerably early stage. Since a previous paper reported that hypocretin-1 values of CSF samples stored at -80º for long periods (8 to 12 years) did not differ from the values of freshly collected samples, the test result from the hypocretin-1 level in the stored CSF sample of Patient 1 is therefore reliable. Compared with a previous report of prepubertal patients with narcolepsy,12 our patients also manifested excessive daytime sleepiness and cataplexy, and the results of nocturnal PSG and MLST were also similar; however, although the CSF hypocretin-1 level in Patient 1 was decreased, the level remained detectable. A recent study showed that CSF hypocretin-1 levels in patients with narcolepsy

Figure 1—Magnetic resonance image: T2-weighted axial (a) and coronal (b) images showing high-intensity signal in the amygdala of the right side (arrow).
and typical cataplexy were reduced (110 pg/mL or less) but not necessarily undetectable. Our results are compatible with that study. Histopathologic study of brain tissue from narcoleptics has revealed marked reductions in the number of hypocretin neurons and the presence of gliosis in the hypocretin cell region, suggesting that autoimmune destruction of the hypocretin neurons may account for most cases of narcolepsy. As the CSF sample of patient 1 was collected at a very early stage, the result might suggest that the CSF hypocretin-1 level was on the way of decline toward the undetectable range. However no subsequent tap was performed, and this speculation was not confirmed.

The core symptoms of narcolepsy in children are similar to those in adults, but manifestation may be different because of maturation factors, which makes the diagnosis challenging. When sleepiness is not mentioned by the patient, attention tends to be focused on hyperactivity and inappropriate behavior with irritability and aggressiveness, which may make physicians consider other disorders. Cataplectic attacks may raise the differential diagnosis of all causes of drop attacks. With respect to these core symptoms, the 2 cases showed relatively distinct clinical pictures compatible with narcolepsy. The MSLT is an objective, well-validated method for confirming the presence of pathologic daytime sleepiness; children may become hypervigilant during the test because of the novel laboratory environment, leading to invalid results. Furthermore, SOREMPs can occur in disorders other than narcolepsy and in healthy adolescents. However, the finding of SOREMPs in patients with excessive sleepiness and cataplexy is significant, suggesting narcolepsy. The first MSLT of both patients revealed no SOREMPs, and the mean sleep latency time for Patient 1 was not typical of narcolepsy. However, the MSLT or the nocturnal PSG conducted several months later showed SOREMPs in both patients. These results indicate that the early diagnosis of narcolepsy in prepubertal children could be difficult due to false-negative MSLT or nocturnal PSG evaluations. Nevertheless, the clinical course may suggest that long-term hypocretin deficiency is required before the occurrence of REM-sleep abnormalities. Measurement of CSF hypocretin-1 level may be useful for early diagnosis and prompt intervention of childhood narcolepsy.

Narcolepsy correlates highly with particular class II HLA-DR and HLA-DQ histocompatibility haplotypes in about 90% of patients with adult-onset narcolepsy, but most people with these haplotypes are not narcoleptic, which indicates that the genetic factor is essential but insufficient to induce human narcolepsy. On the other hand, the existence of twins discordant for narcolepsy suggests that nongenetic, environmental factors have a critical role in the development of narcolepsy. Furthermore, head trauma and encephalitis have recently been suggested to be possible triggering events. In the present cases, Patient 2 reported head contusion before she developed hypersomnia, and Patient 1 had a ganglioma located in the amygdala. As the amygdalo-hypothalamic projections have been demonstrated in reptiles, the same projections may also be considered in mammals. The ganglioma located in the amygdala might have affected the hypothalamus and played some role in the development of narcolepsy in Patient 1. As the period before symptom manifestation is shorter in prepubertal-onset than in adult-onset narcolepsy, accumulation and evaluation of the histories of narcolepsy patients with prepubertal onset might disclose more information about environmental factors.

In conclusion, hypocretin levels in CSF were decreased before the presence of SOREMPs was confirmed by MSLT or PSG in 2 patients with prepubertal narcolepsy with cataplexy. Measurement of CSF hypocretin-1 levels may be useful for early diagnosis and prompt intervention, especially in narcolepsy with prepubertal onset.

REFERENCES


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