Secondary Narcolepsy in Children with Brain Tumors

Carole L. Marcus MBBCh,[1] William H. Trescher MD,[2] Ann C. Halbower MD,[1] and Janita Lutz RPsgT[1]

[1]The Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University; [2]the Division of Neurology and Developmental Medicine, Kennedy Krieger Institute, Baltimore, MD, USA

Summary: We report two cases of children with disabling daytime sleepiness associated with suprasellar tumors and hypothalamic obesity. Multiple sleep latency testing demonstrated features consistent with severe narcolepsy, with sleep latencies of 0.25 and 0.75 minutes, and REM latencies of 2.1 and 1.5 minutes, respectively. An additional patient with hypothalamic damage secondary to a brain tumor, who was thought to be in a vegetative state, had features of narcolepsy on polysomnography. All children responded well to treatment with stimulants. We speculate that secondary narcolepsy associated with hypothalamic tumors is due to damage or loss of hypothalamic hypocretin-containing neurons. In view of the good response to treatment, we recommend that all children with excessive daytime sleepiness and hypothalamic damage be evaluated for narcolepsy.

Key words: Craniopharyngioma; suprasellar tumor; hypocretin

INTRODUCTION

NARCOLEPSY IS A NEUROLOGIC DISORDER OF UNKNOWN ETIOLOGY THAT IS CHARACTERIZED BY EXCESSIVE DAYTIME SLEEPINESS ASSOCIATED WITH CATAPLEXY AND OTHER RAPID EYE MOVEMENT (REM) SLEEP-RELATED PHENOMENA.[1] Human narcolepsy is thought to be caused by an interplay of genetic and environmental factors, and shows a tight association with human leukocyte antigen (HLA) DQB1*0602. Recent animal studies have demonstrated that genetic alterations in either hypocretin ligands or hypocretin receptor-2 can cause narcolepsy in mice[2] and dogs[3]. In humans, mutations in hypocretin-related genes are thought to be rare, but functional impairment of the hypocretin system in human pathology has been demonstrated by observations of reduced hypocretin ligands in the cerebrospinal fluid[4] and brains[5] of narcoleptic subjects.

In addition to the idiopathic form of narcolepsy, secondary narcolepsy has also been diagnosed following central nervous system (CNS) insults such as head injuries.[6] A few case reports have described narcolepsy or cataplexy associated with CNS lesions, including craniopharyngiomas and hypothalamic sarcoid granulomas.[7-9] As hypocretin-containing neurons are located exclusively in the hypothalamus, it is possible that traumatic injury or space-occupying lesions of the hypothalamus can cause narcolepsy. Several recent case reports have described low cerebrospinal fluid hypocretin levels in patients with narcolepsy or hypersomnia related to hypothalamic abnormalities.[10-12] We report two children with the onset of secondary narcolepsy in association with suprasellar tumors and hypothalamic obesity, and an additional patient with a narcolepsy-like state following hypothalamic damage, all presenting within one year at our institution. All children responded well to treatment.

Disclosure Statement
Supported by Grant RR-00052, Pediatric Clinical Research Center, The Johns Hopkins Hospital, Baltimore, MD; and NHLBI grant HL58585.

Submitted for publication June 2001
Accepted for publication February 2002
Address correspondence to: Carole L. Marcus, MBBCh, Division of Pediatric Pulmonology, Park 316, Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287-2533; Tel: (410) 955-2035; Fax: (410) 955-1030; E-mail: cmarcus@welch.jhu.edu

Case #1

The patient was a 16-year-old girl who was referred for evaluation of excessive daytime sleepiness. She had been well until 14 years of age, other than conductive hearing loss for which she wore hearing aids. At 14 years of age, she developed headaches, and gained 40 kg in weight over four months. She was diagnosed with a suprasellar germinoma (Figure 1). The tumor was resected at another institution. Postoperative complications included hemiparesis, panhypopituitarism, and other hypothalamic problems such as temperature instability and obesity due to an insatiable appetite. She was referred to our institution for further care. At initial evaluation two years postoperatively, the patient had severe somnolence to the degree that she would fall asleep during conversations and was unable to pursue normal activities. She went to bed at 20:00 and arose at 06:00. However, she would wake up several times a night because of nocturia related to diabetes insipidus. During the daytime, she would continuously nod off. A trial of methylphenidate 20 mg BID had not resulted in significant changes in alertness. There was a history of mild, continuous snoring without labored breathing or apneic pauses. There was no history of sleep paralysis or hypnagogic hallucinations. Typical cataplectic episodes did not occur. However, the patient had episodes of weakness in her legs, not associated with emotions. During one of these episodes she fell and sprained her ankle. Because of these events, she was confined to a wheelchair. An EMG performed while she was asymptomatic was normal. Medications included nasal desmopressin, thyroxin, and prednisone. There was no family history of excessive daytime sleepiness.

On physical examination, the patient was markedly obese. Weight was 153 kg, and body mass index (BMI) 52 kg/m^2. She was extremely somnolent. Although she was able to stay awake when being directly questioned, she fell asleep as soon as the conversation was directed to her parent. When awake, she was oriented and cognitively intact. Examination of the oropharynx was remarkable for a small amount of tonsillar tissue and mild

Table 1—Polysomnography and MSLT results

	Case 1	Case 2 Study #1	Case 2 Study #2	Case 3
Age (yr)	16	5	-	11
Gender	female	female	-	male
Tumor type	suprasellar germinoma	craniopharyngioma	-	hypothalamic astrocytoma
Cataplexy	atypical	none	-	none
POLYSOMNOGRAM				
Total recording time (min)	498	554	462	544
Sleep efficiency (%)	92	100	98	81
REM latency (min)	3	3	8	4
Arousal index (N/hr)	5.1	7.7	3.6	7.3
Apnea hypopnea index (N/hr)	1.0	10.7	0.1	4.1
MSLT				
Mean sleep latency (min)	0.25	0.75	3.5	0
Range:	0 - 0.5	0 - 3	2.5 - 4.5	0 - 0
Mean REM latency (min)	2.1	1.5	1.1	1.1

REM, rapid eye movement sleep; MSLT, multiple sleep latency test.

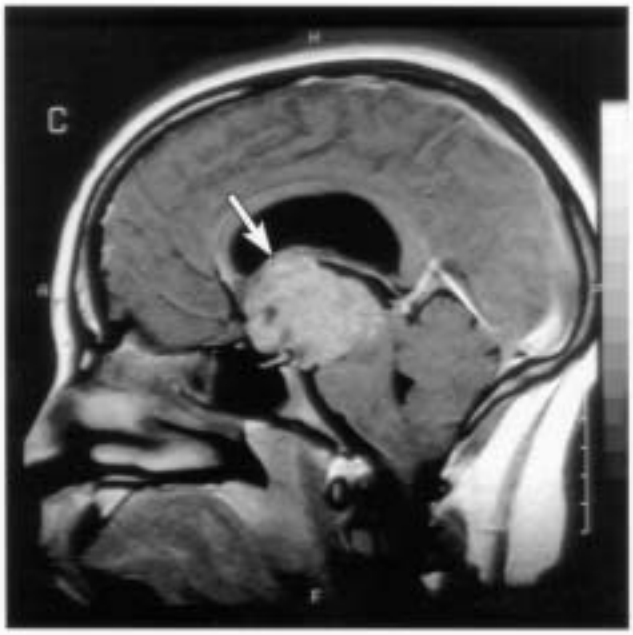

Figure 1—The MRI for patient #1 is shown. The sagittal, T1-weighted, contrast enhanced magnetic resonance image demonstrates a large suprasellar mass (arrow), which on pathology was diagnosed as a germinoma. The tumor displaces the mid-brain and upper portion of the pons. Mild obstructive hydrocephalus of the lateral ventricles is evident, with posterior and superior displacement of the third ventricle and a normal sized fourth ventricle.

crowding of the oropharynx. A mild left hemiparesis was present. The remainder of the examination was normal. Pulmonary function tests, including tests of respiratory muscle strength, were normal.

The patient underwent a sleep study and multiple sleep latency test (MSLT). This showed no evidence of obstructive apnea (Table 1). Although esophageal pressure was not monitored, there was no paradoxical breathing and the arousal index was normal, making it unlikely that she had the upper-airway resistance syndrome. The MSLT was consistent with severe narcolepsy (Table 1). HLA typing was negative for the DR2 and DQB1*0602 antigens. The patient was seen back in clinic and started on modafinil 200 mg a day. In addition, it was thought that the episodes of muscle weakness could be episodes of cataplexy that were atypical in that they were not associated with emotion.[13,14] She was therefore placed on a trial of nortryptiline. On treatment, the patient had a dramatic improvement in daytime sleepiness. On follow-up, she was cheerful and interactive, and remained alert throughout the clinic visit. The episodes of muscle weakness had resolved, and she was now ambulatory. She was attending summer camp, and subsequently returned to school. One year later, she continues to do well.

Case #2

The second patient was a five-year-old child with daytime sleepiness that began one month prior to diagnosis of a craniopharyngioma. The child started sleeping frequently during the day (e.g., she would be found asleep in the coat closet at school). She also developed morning headaches with vomiting. She was diagnosed with the tumor and underwent resection at another institution. Postoperative problems included hypothalamic obesity (the child would eat anything in sight, such as clothing), panhypopituitarism, type II diabetes mellitus, recurrent fevers thought to be central in origin, and hypersomnolence to the point where she was rarely awake. She was referred to our institution for further management. At that time, her mother described snoring and obstructive apneas that had not been present pre-operatively. Of note, the snoring occurred as the child's weight increased.

On examination, the patient was a somnolent child in a wheelchair. When awakened, she was interactive and appropriate. For example, she could recite the alphabet. However, when not being actively stimulated, she immediately lapsed back into

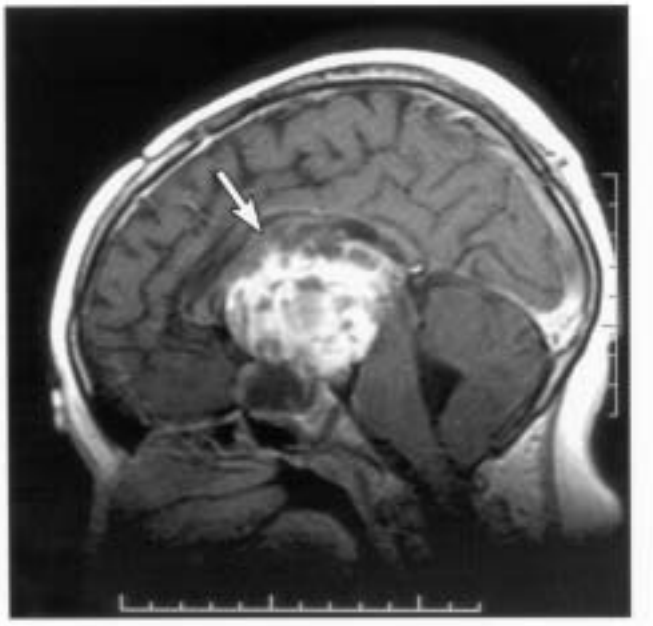

Figure 2—The MRI for patient #3 is shown. The sagittal, T1-weighted, contrast enhanced magnetic resonance image demonstrates a large suprasellar mass, which is a recurrent hypothalamic-optic nerve astrocytoma (arrow). The mass extends into the sella inferiorly and displaces the floor of the third ventricle. The superior aspect of the brainstem is displaced posteriorly. Mild obstructive hydrocephalus of the lateral ventricles is evident, but relatively decompressed with a ventriculo-peritoneal shunt (not seen on this image).

sleep. Her weight was 35 kg, and BMI was 29 kg/m^2. Tonsils were enlarged, and the oropharynx appeared crowded.

A sleep study showed moderate obstructive sleep apnea by pediatric standards[15] (Table 1). The MSLT was consistent with severe narcolepsy (Table 1). During the MSLT, it was impossible to keep the child awake between the naps. Because the child was medically unstable, it was decided to treat the obstructive apnea with bilevel positive pressure and then re-evaluate her to determine the extent to which the obstructive apnea was contributing to her daytime sleepiness. Subsequently, she was discharged home. When re-evaluated in the clinic two months later, her endocrine status had stabilized; however, she had been noncompliant with the positive pressure treatment. A repeat sleep study without positive pressure, and MSLT, showed resolution of the obstructive apnea but persistent findings consistent with narcolepsy (Table 1). The patient was placed on modafinil. As the pediatric dosage has not been established, she was placed on a starting dose of 100 mg a day.

Following this evaluation, the patient had numerous hospitalizations in another city because of recurrent fever and poor diabetic control. Therefore, she was not re-evaluated until six months later, when she was transferred back to our institution for further inpatient management. She was extremely somnolent and had not been using the modafinil. At this point, she also had severe behavioral problems and was angry and combative. She weighed 53 kg. A third sleep study showed that she had no obstruction (apnea index of 0/hr). However, she had mild REM-related desaturation and hypercapnia, which was thought to be due to either obesity-related restrictive lung disease or a component of central hypoventilation. The patient was unable to cooperate with pulmonary function testing or ventilatory response testing, and did not tolerate bilevel pressure despite behavioral conditioning. She was therefore treated with supplemental oxygen during sleep. The dosage of stimulant drugs was titrated to achieve adequate alertness. She required modafinil 200 mg a day and methylphenidate 20 mg TID. On this regimen, she was alert and interactive during the day. The patient was transferred back to her home town and has not returned for further follow-up.

Case #3

The third patient was an 11-year-old boy referred for evaluation of a persistent vegetative state following brain tumor resection and CNS hemorrhage. The child was initially diagnosed at one year of age with an astrocytoma involving the optic nerve and hypothalamus. This was treated with tumor debulking and chemotherapy. Over the subsequent decade, he underwent two further debulking procedures, several ventriculoperitoneal shunt placements and cranial radiotherapy. He developed growth hormone deficiency and precocious puberty secondary to his tumor. Despite his medical problems, he had a functional lifestyle. He was in special education, and was able to ride a bicycle. Several months prior to his presentation to us, he developed increasing sleepiness, and would fall asleep while on the toilet or when playing with friends. One day prior to admission, he developed lethargy, disorientation, and urinary incontinence, and underwent a shunt revision. He continued to have intermittent lethargy postoperatively. A repeat MRI was performed. This showed a large suprasellar mass (Figure 2). He underwent further tumor debulking and insertion of a new ventriculoperitoneal shunt. Surgery was complicated by hemorrhage. Postoperatively, the patient was nonresponsive and had a Glasgow coma scale of 8. He developed hypothyroidism and inappropriate antidiuretic hormone secretion. He was transferred to a rehabilitation center, where he remained in a vegetative state. The child appeared to be asleep most of the day, but would open his eyes when stimulated. He did not speak or obey commands, and was fed by nasogastric tube. His mental state did not improve during his two months in rehabilitation.

Because of our recent experience with the other two patients, nocturnal and daytime polysomnography was performed. A formal MSLT could not be done as the patient could not be kept awake between naps; however, recordings were performed for 20 minutes every two hours. The nocturnal study showed a few hypopneas with mild arterial oxygen desaturation (Table 1). The EEG was abnormal, with generalized slowing and increased amplitude; thus it was difficult to distinguish the different nonREM sleep stages. Sleep was fragmented, with 16 short REM cycles. The daytime study showed frequent REM periods. HLA typing was negative for the DR2 and DQB1*0602 antigens.

Due to our past experience, a trial of modafinil was recommended. However, the patient's primary physician elected not to do this. The patient was discharged home. It was decided not to treat his mild sleep-disordered breathing, due to his vegetative state and complicated home care regimen.

The child was seen in the sleep clinic three weeks following discharge. At that time, he remained in a vegetative state. He would open his eyes for a maximum of fifteen minutes at a time. He was placed on modafinil 200 mg a day. One month later, he

Table 2—Clinical and MSLT characteristics of children diagnosed with narcolepsy at out institution

	Narcolepsy	Brain Tumor
N	13	3
Age at diagnosis (yr)	11 (4)	11 (6)
Range:	5 - 18	5 - 16
Cataplexy (N, %)	3 (23)	1 atypical (33)
Sleep Latency (min):	5.3 (3.2)	0.3 (0.4)*
Range:	0.9 - 11.4	0 - 0.75
# REM-onset naps (out of 4)	4±1	4±0**
REM latency (min):	4.4 (3.8)	1.6 (0.5)**
Range:	0.1 - 11.3	1.1 - 2.1

*p<0.001
**p<0.05
REM, rapid eye movement sleep
All data displayed as mean (SD) except where otherwise indicated.

returned for follow-up. He had improved dramatically. He was sleeping for nine hours a night. During the day, he would stay awake for four hours at a time, and then nap for 45 minutes. He was able to ambulate with support and feed by mouth. He had returned to school. Although he talked very little, he was able to use a computer. Repeat follow-up two months later showed continued improvement. On a regimen of modafinil 200 mg a day and methylphenidate 5 mg BID, the patient was remaining awake all day except for a one-hour nap.

Retrospective Survey of Pediatric Patients with Suprasellar Tumors

Following identification of these cases, we reviewed patients who had suprasellar tumors resected at our institution, in order to determine the frequency of excessive daytime sleepiness as a complication of suprasellar tumors. Sixteen pediatric patients living within the USA had been treated at our institution. A letter was sent to the parents of these patients, followed by a telephone call. Four patients no longer resided at the address of record, and two families did not respond. Of the ten remaining patients, nine families stated that the child had no daytime sleepiness. One family from another state thought that their child was somewhat sleepy, but did not want to return for evaluation. Of note, only one of these children was morbidly obese. The others had hypopituitarism but no other evidence of hypothalamic abnormalities.

Retrospective Review of Pediatric Patients with Narcolepsy

The records of all pediatric patients diagnosed with idiopathic narcolepsy at our institution since the inception of our database were reviewed (Table 2). These patients were all in good general health, presented with a chief complaint of excessive daytime sleepiness, had normal overnight sleep studies, a reduced sleep latency as well as ≥ 2 REM-onset naps on MSLT, and no other cause for their somnolence.[1] The mean sleep latency and REM latency on MSLT in these patients was generally higher than in the children with suprasellar tumors, but some were equally severe.

DISCUSSION

We report three pediatric cases with a severe narcolepsy-like condition associated with suprasellar tumors and hypothalamic abnormalities. All patients had disabling symptoms that improved dramatically on stimulants. The incidence of narcolepsy associated with hypothalamic lesions in children is not clear. A retrospective survey of patients at our institution with suprasellar tumor resections and hypopituitarism but no other evidence of hypothalamic disorders did not reveal additional patients with histories of excessive daytime sleepiness. Nevertheless, the potential for therapeutic benefit warrants consideration of secondary narcolepsy in all children with hypersomnolence related to hypothalamic lesions.

One previous study evaluated the sleep patterns of children with a history of craniopharyngiomas.[16] Two of ten children reportedly had decreased sleep latencies on MSLT. However, details of the MSLT, including the presence or absence of REM sleep, were not provided. It is not known if any of these children were obese. Two previous case reports each described narcolepsy in a patient with craniopharyngioma and obesity.[7,8] In addition, Aldrich and Naylor[7] described two patients with hypothalamic lesions (one due to sarcoidosis and one of unknown etiology) and obesity who developed narcolepsy.

Narcolepsy has recently been shown to be due to a deficiency in hypocretin. In familial cases of canine narcolepsy, the deficiency in the hypocretin system is genetic in nature.[3] Humans with idiopathic narcolepsy have a decreased number of hypocretin-producing neurons on autopsy, which is thought to be secondary to a degenerative process.[5] Although there is no direct evidence, we hypothesize that our patients had damage to their hypocretin-containing neurons due to their tumor or as a result of surgery, resulting in secondary narcolepsy. It is of interest to note that the patients in our series, and those reported in the literature, all had obesity related to their hypothalamic lesions. This may also be related to hypocretin deficiency. Hypocretin plays a role in feeding and metabolic control. Body weight has been found to be increased in both transgenic mice and narcoleptic humans with low hypocretin levels.[2,4]

Tumors in the suprasellar region of the brain are relatively common in childhood. The most common type is a craniopharyngioma, which is estimated to account for 9% of intracranial tumors in children.[17] Suprasellar tumors are often benign, but are associated with a high morbidity due to encroachment on such vital areas as the pituitary, optic chiasm and hypothalamus. Common complications, due either to the tumor itself or as a result of surgical resection, include visual field defects, panhypopituitarism and obesity secondary to an insatiable appetite. If these patients develop excessive daytime sleepiness, it is often presumed to be due to their endocrine and metabolic abnormalities, or to obesity-related obstructive sleep apnea, rather than narcolepsy.

Two of our patients had evidence of mild to moderate sleep-disordered breathing on polysomnography. However, we do not think that this explained their hypersomnolence. Most children with obstructive apnea, unlike adults, do not have frequent arousals during sleep[18] and do not manifest daytime sleepiness.[19] Furthermore, in case #2, hypersomnolence persisted despite resolution of obstructive sleep apnea. In this child, it is unclear why the obstructive apnea resolved. However, it may have been due

to the improvement in her endocrine and metabolic status. In case #3, the daytime sleepiness improved with modafinil although the sleep-disordered breathing had not been treated. It is unlikely that the narcolepsy condition in these patients was incidental to the tumors. Although narcolepsy occurs in the pediatric population, it is rare.[20-22] In all of our patients, symptoms of hypersomnolence occurred in close association with the development of symptoms related to the tumor, or the resection of the tumor. Furthermore, HLA typing was negative for the DR2 and DQB1*0602 antigens in the two patients tested.

One of our patients had cataplexy that was atypical in that it was not associated with emotion. The episodes resolved with nortryptiline. Atypical continuous cataplexy has been reported in association with a hypothalamic/brainstem tumor,[13] and isolated cataplexy in a child with a pontine tumor.[14] Cataplexy occurs less commonly in children than adults, and may not be present during the initial years of the disease.[21,23,24] For example, in one large series of 51 children with narcolepsy and cataplexy, excessive daytime sleepiness preceded the onset of cataplexy in 80% of children.[21] Thus, it is possible that the other children in this series will develop cataplexy in the future. In our retrospective review of pediatric narcolepsy patients at our institution, 23% were noted to have cataplexy (Table 2).

In conclusion, we report three cases of secondary narcolepsy in children with hypothalamic lesions and evidence of widespread hypothalamic damage. A review of the literature and a retrospective survey of other cases of suprasellar tumors suggest that narcolepsy is more likely to occur in patients with generalized hypothalamic damage (in particular, those with severe obesity) than patients with isolated suprasellar lesions. We speculate that this could be due to damage of hypocretin-containing neurons. Despite the severity of their condition, the children responded well to conventional treatment of narcolepsy, with an improvement in their quality of life. We therefore recommend that all children with hypothalamic lesions and daytime sleepiness be evaluated with polysomnography and multiple sleep latency testing.

ACKNOWLEDGMENTS

We thank Benjamin Carson, M.D. for his help, Dana Foer, PA-C for assistance in contacting patients, James Christenson M.D. and Beth Wieczorek C.P.N.P. for referring patients, and Paul Poole, R.Psg.T. and Patricia Galster, R.Psg.T. for their help in conducting and scoring the sleep studies.

REFERENCES

1. American Sleep Disorders Association. Narcolepsy. In: diagnostic classification steering committee, Thorpy MJ, ed. The international classification of sleep disorders: Revised. Diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association, 1997:38-43.
2. Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. Neuron 2001;30(2):345-354.
3. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene [see comments]. Cell 1999;98(3):365-376.
4. Nishino S, Ripley B, Overeem S, Nevsimalova S, Lammers GJ, Vankova J et al. Low cerebrospinal fluid hypocretin (Orexin) and altered energy homeostasis in human narcolepsy. Ann Neurol 2001;50(3):381-388.
5. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000;27(3):469-474.
6. Lankford DA, Wellman JJ, O'Hara C. Posttraumatic narcolepsy in mild to moderate closed head injury. Sleep 1994;17(8 Suppl):S25-S28.
7. Aldrich MS, Naylor MW. Narcolepsy associated with lesions of the diencephalon. Neurology 1989;39(11):1505-1508.
8. Schwartz WJ, Stakes JW, Hobson JA. Transient cataplexy after removal of a craniopharyngioma. Neurology 1984;34(10):1372-1375.
9. Rubinstein I, Gray TA, Moldofsky H, Hoffstein V. Neurosarcoidosis associated with hypersomnolence treated with corticosteroids and brain irradiation. Chest 1988;94(1):205-206.
10. Arii J, Kanbayashi T, Tanabe Y, Ono J, Nishino S, Kohno Y. A hypersomnolent girl with decreased CSF hypocretin level after removal of a hypothalamic tumor. Neurology 2001;56(12):1775-1776.
11. Melberg A, Ripley B, Lin L, Hetta J, Mignot E, Nishino S. Hypocretin deficiency in familial symptomatic narcolepsy. Ann Neurol 2001;49(1):136-137.
12. Scammell TE, Nishino S, Mignot E, Saper CB. Narcolepsy and low CSF orexin (hypocretin) concentration after a diencephalic stroke. Neurology 2001;56(12):1751-1753.
13. Stahl SM, Layzer RB, Aminoff MJ, Townsend JJ, Feldon S. Continuous cataplexy in a patient with a midbrain tumor: the limp man syndrome. Neurology 1980;30(10):1115-1118.
14. D'Cruz OF, Vaughn BV, Gold SH, Greenwood RS. Symptomatic cataplexy in pontomedullary lesions. Neurology 1994;44(11):2189-2191.
15. American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. Am J Respir Crit Care Med 1996;153:866-878.
16. Palm L, Nordin V, Elmqvist D, Blennow G, Persson E, Westgren U. Sleep and wakefulness after treatment for craniopharyngioma in childhood; influence on the quality and maturation of sleep. Neuropediatrics 1992;23(1):39-45.
17. DeVile CJ, Grant DB, Hayward RD, Stanhope R. Growth and endocrine sequelae of craniopharyngioma. Arch Dis Child 1996;75(2):108-114.
18. McNamara F, Issa FG, Sullivan CE. Arousal pattern following central and obstructive breathing abnormalities in infants and children. J Appl Physiol 1996;81:2651-2657.
19. Carroll JL, Loughlin GM. Obstructive sleep apnea syndrome in infants and children: Clinical features and pathophysiology. In: Ferber R, Kryger M, editors. Principles and practice of sleep medicine in the child. Philadelphia, PA: W.B. Saunders Company, 1995:163-191.
20. Kotagal S, Hartse KM, Walsh JK. Characteristics of narcolepsy in preteenaged children. Pediatrics 1990;85(2):205-209.
21. Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. Ann Neurol 1998;43(1):135-142.
22. Young D, Zorick F, Wittig R, Roehrs T, Roth T. Narcolepsy in a pediatric population. Am J Dis Child 1988;142(2):210-213.
23. Wise MS. Childhood narcolepsy. Neurology 1998;50(2Suppl 1):S37-S42.
24. Kotagal S. A developmental perspective on narcolepsy. In: Loughlin GM, Carroll JL, Marcus CL, editors. Sleep and breathing in children: a developmental approach. New York: Marcel Dekker, 2000:347-362.