

Hypersomnia Caused by Isolated Angiitis of the CNS

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Abstract

A 42-year-old woman presented gradual development of hypersomnia and memory disturbance. T2-weighted and FLAIR MRI scans revealed a high intensity abnormality in the hypothalamus. Stereotactic brain biopsy specimen revealed prominent infiltration of the lymphocytes in the vessel walls. Since there was no evidence of systemic angiitis, the diagnosis of isolated angiitis of the CNS (IAC) was made. Polysomnographic study showed decreased REM sleep and increased stage I sleep. Orexin A in the CSF was decreased. Hypersomnia and a decrease of the CNS orexin A improved after corticosteroid therapy. Hypersomnia can be an initial symptom of IAC if it involves the hypothalamus. (Internal Medicine 44: 883–885, 2005)

Key words: isolated angiitis of the CNS, hypersomnia, orexin A, MLST

Introduction

Isolated angiitis of the CNS (IAC) was described in 1959 as non-infectious granulomatous angiitis with predilection for smaller leptomeningeal and intraparenchymal arteries of the central nervous system involving the small and medium sized arteries in the brain (1). The lesion is focal or segmental and involves the leptomeninges and gray and white matter (1). In IAC extracranial vessels are almost never involved, and thus it is clinically characterized by headache, encephalopathy and multifocal neurological deficits depending on the location of the vascular lesions in the central nervous system, but general symptoms such as fever, weight loss, anorexia and vomiting are also occasionally present. We describe a patient who presented gradual development of daytime sleepiness, a rare initial symptom of this disease, that

was associated with MRI abnormalities in the hypothalamus and low levels of orexin A in the CSF.

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Case Report

A 42-year-old woman was admitted to our hospital because of gradual development of fatigue, daytime sleepiness and later memory disturbance. The patient was a healthy, married woman except for infrequent seizures until 2 years prior to admission when she started complaining of chronic fatigue. Since 1 year prior to admission, she has felt very sleepy and had a long nap, which lasted almost all day long except for the time for preparing and having a meal. Six months before admission she started having an impairment of recent memory. Neither snoring nor sleep apnea was noticed at night. In the past medical history, she has had infrequent seizure episodes for over 30 years. The patient has been taking 500 mg of carbamazepine, 200 mg of phenytoin and 20 mg of phenobarbital daily with blood levels of 2.8 µg/ml, 6.9 µg/ml and 2.8 µg/ml, respectively, at the time of admission. On physical examination, she was mildly obese (BMI =27.43) but otherwise the findings were unremarkable. On neurological examination, cranial nerves, motor and sensory system, and cerebellar functions were normal. She was disoriented in place and time, but no aphasia or apraxia was present. She appeared asthenic, but at least managed to respond to the questions. There was no hallucination, no delusion or no confabulation. The Mini-Mental state score was 22/30.

The following laboratory tests were normal or negative: complete blood count, platelet count, electrolytes, liver function tests, blood glucose, BUN and creatinine, urinalysis, C-reactive protein (CRP), ESR, serum vitamins (vitamin B1 and B12) and folate, antinuclear antibody (anti-double stranded DNA, anti-Sm), anticardiolipin antibody, β₂ glyco-

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protein, cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), perinuclear -ANCA, angiotensin-converting enzyme, VDRL, treponema pallidum hemagglutination assay (TPHA) test, and antibodies against hepatitis B and C, and HIV. As for endocrine studies the serum gonadotropin, prolactin, and adrenocorticotrophic hormone levels were all normal. Free T3 and thyroid stimulating hormone were normal but the free T4 level was slightly decreased (0.46 ng/dl: normal range of 0.98–1.77 ng/dl). The CSF protein (77.3 mg/dl) and cell count (6/μl) were mildly elevated, and glucose (47 mg/dl), total IgG (12.3 mg/dl) and IgG index (0.52) were normal. The presence of oligoclonal IgG bands of CSF was not tested. CSF orexin A was significantly decreased [117 pg/ml: normal range of 280±33.0 pg/ml (2)].

EEG showed poorly organized background activity with slow posterior dominant rhythm (7–8 Hz), generalized continuous irregular theta waves (5–7 Hz), and intermittent rhythmic delta waves (2–3 Hz), which occurred every 10–50 seconds in the bilateral frontal areas. Sporadic sharp transients were also observed in the left parietal area. T2-weighted and FLAIR MRI scans of the brain revealed high intensity abnormality in the hypothalamus and bilateral basal ganglia that was slightly enhanced by gadolinium (Fig. 1). In addition, there was cortical malformation with pachygyria in the posterior hemispheres. MR angiography did not reveal any stenosis or aneurysm in the major arteries. Overnight polysomnogram (PSG) showed decreased occurrence of REM sleep and increased stage I sleep. In the multiple sleep latency test (MSLT), mean sleep latency among five trials was 7.5 minutes with no sleep-onset REM (Table 1). Stereotactic brain biopsy was performed for the diagnostic purposes. The biopsy specimen from the lateral part of the right caudate nucleus showed the prominent infiltration of the lymphocytes in the vascular walls of arterioles (Fig. 2A) and in the perivascular area of small vessels (Fig. 2B). The lymphocytes appeared normal in shape and did not show any evidence of neoplasia in immunohistochemistry analysis with T cell and B cell markers. Lymphocytes positive for both B-cell and T-cell markers were observed in the vascular walls and perivascular regions. Indistinct vessel wall with prominent endothelial cells, perivascular reactive gliosis with astrocytes, ischemic neurons and neuropil edema were also observed. No macrophages with periodic acid-Schiff (PAS)-positive sickle or gram-positive bacilli were detected in the tissue. In the electron microscopic study, no virus, fungus or bacterial organisms were identified. Since brain biopsy specimens fulfilled the pathological criteria for the definite diagnosis proposed by Alrawi et al (3) and since there was no evidence of systemic angitis, the diagnosis of IAC was made, and the patient was treated by steroid pulse therapy (intravenous administration of 1 g/day of methylprednisolone for 3 days) followed by oral administration of prednisone. Although disorientation and impairment of recent memory had persisted, daytime sleepiness and daily behavior significantly improved. MRI findings of high intensity abnormality in the hypothalamus and bilateral ganglia with T2-WI and FLAIR image did

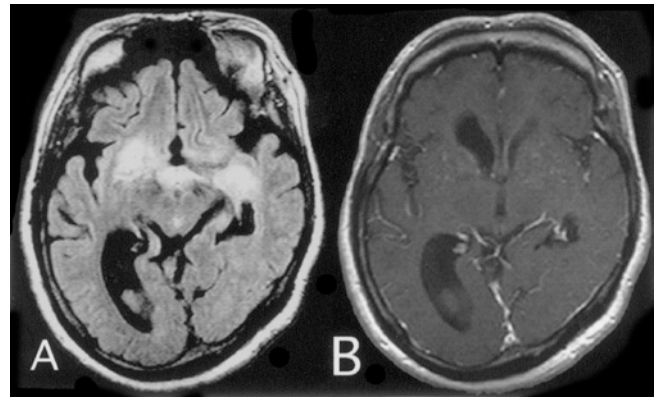


Figure 1. FLAIR (A) and gadolinium-enhanced T1-weighted MRIs (B) obtained 6 months after the clinical onset. Note: high intensity abnormality in the hypothalamus and bilateral basal ganglia (A). The lesion in the basal ganglia is slightly enhanced by gadolinium. In addition, cortical malformation with pachygyria and enlarged ventricle are also seen mainly in the posterior hemispheres (B).

Table 1. Sleep Study in the Patient with Isolated Angitis in the CNS

Polysomnograph	
Sleep duration (min)	512.5
Sleep efficiency (TST% of TIB)	76.0
Sleep latency (min)	22.0
REM latency (min)	213.5
Stage Wake (% of TST)	17.8
Stage I (% of total sleep time TST)	22.5
Stage II (% of TST)	25.9
Stage III+IV (% of TST)	20.6
REMs (% of TST)	8.6
Multiple sleep latency test	
Mean sleep latency (min)	7.5
Occurrence of sleep onset REM	0/5

TST: Total sleep time, TIB: Time in bed.

not improve apparently. Protein level in the CSF decreased from 77.3 mg/dl to 62.3 mg/dl and CSF orexin A increased from 117 pg/ml to 192 pg/ml after the treatment.

Discussion

IAC is often fatal unless treated with immunosuppressive agents, and thus a prompt diagnosis is very important (3). The clinical features of IAC are protean and can be focal or diffuse. Transient or persistent hemiparesis, sensory loss, ataxia, seizures, cranial neuropathies and/or paraparesis have been reported as focal symptoms. General neurological symptoms include headache, cognitive decline, confusion, fluctuating level of consciousness, lethargy and malaise. The

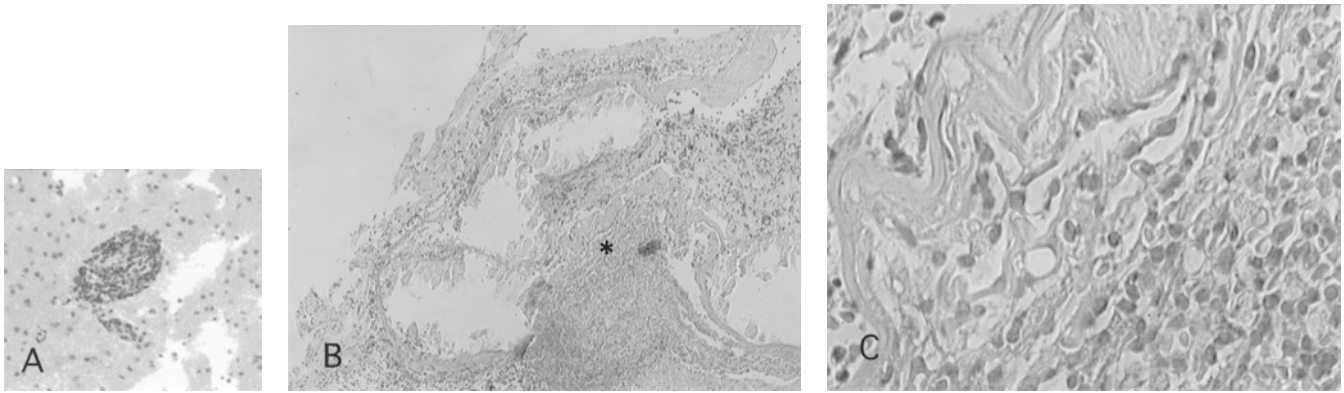


Figure 2. A brain biopsy specimen obtained from the right basal ganglia. Note: prominent infiltration of the lymphocytes within the vascular walls of small vessels (A) (HE stain, $\times 600$) and arterioles (B) (HE stain, $\times 250$), that were accompanied by the small reactive gliosis with astrocytes. (C) Magnification of the region indicated by an asterisk in (B) (HE stain, $\times 2000$).

most common symptom is reported to be headache with encephalopathy accompanied by multifocal neurological signs (4, 5). Its clinical and radiologic features resembling tumor, infection, dementia or stroke can often impede immediate and correct diagnosis of IAC and subsequently definite diagnosis not infrequently needs a brain biopsy.

The current patient presented excessive daytime sleepiness and dementia. She was disoriented in time and place and recent memory was impaired. However, consciousness was not disturbed. The patient's symptoms slowly progressed. We confirmed the abnormality of sleep architecture by PSG and decreased sleep latency by MSLT. Other causes of daytime sleepiness such as obstructive sleep apnea, hypothyroidism and infectious persistent encephalitis were excluded and brain biopsy specimen showed the angiitis. T2-weighted and FLAIR MRI scans of the brain revealed high intensity abnormality in the hypothalamus. The association between sleep and hypothalamus has been well documented in patients suffering from the viral encephalitis epidemic in 1918. They presented excessive sleep and post-mortem analysis revealed damage in the posterior hypothalamus (6, 7). Hypocretins/orexins are newly identified peptides of hypothalamic origin, which have the role in feeding and sleep regulation (8). Orexin A deficiency is related to the sleep disorder which causes excessive daytime sleepiness such as narcolepsy. Orexins are also involved in neuroendocrine functions and stress reactions, central pain perception, autonomic function and ischemic brain changes. The CSF orexin level is found to be decreased in several neurological conditions such as narcolepsy, systemic lupus erythematosus (9, 10) multiple sclerosis (11, 12), Whipple's disease (13) and depression (14). Two reports on patients with multiple sclerosis described the manifestation of hypersomnia with hypothalamic lesion. When considering the responsiveness of the decreased CSF orexinA level to steroid pulse therapy in the present patient, it was most likely due to the hypothalamic involvement of IAC, which may cause daytime sleepiness.

Although excessive daytime sleepiness can be associated with any chronic infections of the CNS such as encephalitis lethargica, it is noteworthy that IAC can cause this symptom if the hypothalamus is involved, as in the present patient.

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