Symptomatic Narcolepsy in Patients With Neuromyelitis Optica and Multiple Sclerosis

New Neurochemical and Immunological Implications

Takashi Kanbayashi, MD, PhD; Takayoshi Shimohata, MD, PhD; Ichiro Nakashima, MD, PhD; Hiroaki Yaguchi, MD; Ichiro Yabe, MD, PhD; Masatoyo Nishizawa, MD, PhD; Tetsuo Shimizu, MD, PhD; Seiji Nishino, MD, PhD

Objective: To characterize factors that contribute to symptomatic narcolepsy and excessive daytime sleepiness in neuromyelitis optica and multiple sclerosis.

Setting: Japanese university hospitals.

Design: Case study.

Patients: Seven Japanese patients whose initial diagnoses were multiple sclerosis and who were exhibiting excessive daytime sleepiness.

Main Outcome Measures: Lesions on magnetic resonance imaging, cerebrospinal fluid hypocretin-1 levels, and serum anti–aquaporin 4 (AQP4) antibody titer.

Results: Bilateral and symmetrical hypothalamic lesions associated with marked or moderate hypocretin deficiency were found in all 7 cases. Four of these patients met the International Classification of Sleep Disorders 2 narcolepsy criteria. Three patients, including 2 patients with narcolepsy, were seropositive for anti-AQP4 antibody and diagnosed as having neuromyelitis optica-related disorder.

Conclusion: Since AQP4 is highly expressed in the hypothalamic periventricular regions, an immune attack on AQP4 may be partially responsible for the bilateral and hypothalamic lesions and hypocretin deficiency in narcolepsy/excessive daytime sleepiness associated with autoimmune demyelinating diseases.

Arch Neurol. 2009;66(12):1563-1566

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, and other rapid eye movement sleep abnormalities.1 The idiopathic form of narcolepsy with cataplexy is highly associated with a deficiency in a hypothalamic neuropeptide, hypocretin/orexin.1,2 The hypocretin deficiency is possibly due to the postnatal cell death of hypocretin-containing neurons. Since narcolepsy is also tightly associated with HLA antigen positivity (HLA DR2/DQB1*0602), an involvement of autoimmune mechanisms in its etiology is suggested, but this has not been proven yet.1,4

Narcolepsy also occurs during the course of various neurological conditions (ie, symptomatic narcolepsy or narcolepsy due to medical conditions), and inherited disorders, tumors, and head trauma are the 3 most frequent causes for symptomatic cases.3 Interestingly, however, a recent meta-analysis indicated that 10 of 116 symptomatic cases of narcolepsy are associated with multiple sclerosis (MS), a disease of autoimmune demyelination. Symptomatic narcoleptic cases consist of heterogeneous disease conditions, but the hypocretin systems are often impaired.2,3 Gaining the basic knowledge of symptomatic narcolepsy in immune-mediated conditions will be not only useful for selecting the most appropriate treatment and predicting the prognosis of the disease but also for understanding the etiological mechanism of narcolepsy.

REPORT OF CASES

We recently had 7 cases of EDS in Japanese patients occurring in the course of MS or neuromyelitis optica (NMO) with symmetrical hypothalamic inflammatory lesions together with hypocretin ligand deficiency,4,8 which contrasts with the characteristics of classic MS cases (Table). Cerebrospinal fluid (CSF) hypocretin-1 levels in these patients were markedly (n=4; ≤110 pg/mL) or moderately (n=3;
and was negative for DQB1 antigen was evaluated in only 2 cases (case 2 and case 4) in patients thus met the criteria for narcolepsy due to medical condition. Six of these patients were female, and 4 had either or both optic neuritis or spinal cord lesions or significantly increased with marked improvements of EDS and hypothalamic lesions in all 6 patients. By immunological evaluations, we found that 3 of 7 patients were anti–aquaporin 4 (AQP4) antibody positive, thus being diagnosed with an NMO-related disorder.

110 to 200 pg/mL) reduced (Table). Four patients thus met the International Classification of Sleep Disorders 2 criteria for narcolepsy due to medical condition, and 3 patients met the criteria for hypersomnia due to medical condition. Six of these patients were female, and 4 had either or both optic neuritis or spinal cord lesions, sharing the clinical characteristics of NMO. HLA antigen was evaluated in only 2 cases (case 2 and case 4) and was negative for DQB1. Repeated evaluations of the hypocretin status were carried out in 6 patients, and CSF hypocretin-1 levels returned to the normal levels or significantly increased with marked improvements of EDS and hypothalamic lesions in all 6 patients. By immunological evaluations, we found that 3 of 7 patients were anti–aquaporin 4 (AQP4) antibody positive, thus being diagnosed with an NMO-related disorder.

COMMENT

Narcolepsy associated with patients with MS was reported several decades ago. Since both conditions are associated with HLA-DR2 positivity, an autoimmune target on the same brain structures has been proposed to be a common etiology for both diseases. However, the discovery of the selective loss of hypothalamic hypocretin neurons in idiopathic narcolepsy indicates that narcolepsy in patients with MS coincidently occurs when MS plaques appear in the hypothalamic area and there is secondary damage to the hypocretin/orexin neurons. Supporting this interpretation, the hypocretin system is not impaired in patients with MS who do not exhibit narcolepsy, although patients with MS frequently show other sleep problems, such as insomnia, parasomnia, and sleep-related movement disorders. Nevertheless, it is also the case that a subset of patients with MS predominantly shows EDS and rapid eye movement sleep abnormalities, and it is likely that specific immune-mediated mechanisms may be involved in these cases.

Interestingly, 3 of our 7 patients were anti–AQP4 antibody positive, and these patients were diagnosed as having an NMO-related disorder. Carlander et al also reported a case of a white female with NMO who was anti–AQP4 antibody positive and had associated EDS and hypocretin deficiency (Table). These results suggest a functional relation between AQP4 and hypothalamic damage.

Aquaporin 4, a member of the aquaporin superfamily, is an integral membrane protein that forms pores in the membrane of biological cells. Aquaporins selectively conduct water molecules in and out of the cell while preventing the passage of ions and other solutes and are known as water channels. Aquaporin 4 is expressed in nonneuronal structures such as astrocytes and ependymocytes but is absent from neurons. Recently, the NMO-IgG autoantibody, which can be detected in the serum of patients with NMO, has been shown to selectively bind to AQP4.

Table. Demographic and Clinical Characteristics of Patients With MS/NMO With Narcolepsy/EDS

<table>
<thead>
<tr>
<th>Case/Sex/Age, y</th>
<th>1/F/45b</th>
<th>2/F/21b</th>
<th>3/F/43c</th>
<th>4/F/35b</th>
<th>5/F/45b</th>
<th>6/F/54c</th>
<th>7/M/61</th>
<th>0/F/49b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis</td>
<td>MS</td>
<td>MS</td>
<td>NMO</td>
<td>NMO</td>
<td>NMO</td>
<td>MS</td>
<td>MS</td>
<td>NMO</td>
</tr>
<tr>
<td>Hypothalamic lesion</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EDS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>REM abnormality</td>
<td>No data</td>
<td>SOREMPs</td>
<td>No data</td>
<td>SOREMPs</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Hypocretin-1 level, pg/mL</td>
<td>&lt;40</td>
<td>&lt;40</td>
<td>190</td>
<td>91</td>
<td>106</td>
<td>184</td>
<td>173</td>
<td>158</td>
</tr>
<tr>
<td>Hypocretin-1 level at remission, pg/mL</td>
<td>167</td>
<td>221</td>
<td>291</td>
<td>290</td>
<td>345</td>
<td>No data</td>
<td>279</td>
<td>874d</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spinal cord lesion</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Long spinal cord lesion</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AQP4 Ab</td>
<td>-e</td>
<td>-e</td>
<td>+e</td>
<td>+1</td>
<td>+f</td>
<td>-f</td>
<td>-f</td>
<td>+</td>
</tr>
<tr>
<td>Laboratory test and the initiation of treatment</td>
<td>CSF tap</td>
<td>6 wk</td>
<td>10 d</td>
<td>3 wk</td>
<td>2 mo</td>
<td>3 wk</td>
<td>2 wk</td>
<td>8 d</td>
</tr>
<tr>
<td>Serum tap</td>
<td>6 wk</td>
<td>10 d</td>
<td>3 wk</td>
<td>2 mo</td>
<td>5.5 mo</td>
<td>3 wk</td>
<td>2 wk</td>
<td>8 d</td>
</tr>
<tr>
<td>MRI</td>
<td>6 wk</td>
<td>10 d</td>
<td>4 wk</td>
<td>1.5 mo</td>
<td>3 wk</td>
<td>3 wk</td>
<td>3 wk</td>
<td>9 d</td>
</tr>
<tr>
<td>Treatment</td>
<td>6.5 wk</td>
<td>11 d</td>
<td>6 wk to</td>
<td>No</td>
<td>3 wk</td>
<td>2-5 wk</td>
<td>7 d-5 wk</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Ab, antibody; AQP4, aquaporin 4; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ICSDII, International Classification of Sleep Disorders 2; MRI, magnetic resonance image; MS, multiple sclerosis; NMO, neuromyelitis optica; REM, rapid eye movement; SOREMP, sleep-onset rapid eye movement period; +, positive; −, negative.

a Levels of CSF hypocretin-1 for all 7 Japanese cases were measured at Akita University. Informed consent was obtained from subjects, and the local ethics committee approved CSF hypocretin-1 measures.
b Met ICSDII criteria for narcolepsy due to medical condition.
c Met ICSDII criteria for hypersomnia due to medical condition.
d Before the episode.
e Anti–human AQP4 Ab was measured at Tohoku University.17
f Anti–human AQP4 Ab was measured at Niigata University.11

dream periods; /H11001
Since AQP4 is enriched in periventricular regions in the hypothalamus where hypocretin-containing neurons are primarily located, symmetrical hypothalamic lesions associated with reduced CSF hypocretin-1 levels in our 3 NMO cases with anti–AQP4 antibody (together with the Carlander et al case) might be caused by the im-

Figure. Magnetic resonance imaging findings (fluid-attenuated inversion recovery [FLAIR] [A-C, F, and G] or T2 weighted [D and E]) of cases 1 through 7. A typical horizontal slice including the hypothalamic periventricular area from each case is presented. AQP4 indicates aquaporin 4; +, positive.
its related disorders. None of our cases exhibited cata-
esiologic mechanisms that cause the bilateral hypothalamic
ease, and the assay was not standardized among the insti-
tobidirectional antibodies who presented with recurrent hyporesin, reduced orexin (hypocretin) level, and symmetrical hypothalamic lesions. Sleep Med. 2009;10(2):253-255.


