Symptomatic Narcolepsy in Patients With Neuromyelitis Optica and Multiple Sclerosis

New Neurochemical and Immunological Implications

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**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. 

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**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, 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;
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.

110 to 200 pg/mL) reduced (Table) (Figure). 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 antigens were evaluated in only 2 cases (case 2 and case 4) and was negative for DQB1 antigen was evaluated in only 2 cases (case 2 and case 4). Six of these patients were female, and 3 patients met the criteria for hypersomnia due to medical condition. Three patients were anti–aquaporin 4 (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.

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/43b</th>
<th>4/F/35b</th>
<th>5/F/42b</th>
<th>6/F/54c</th>
<th>7/M/81</th>
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<tr>
<td>Clinical diagnosis</td>
<td>MS</td>
<td>MS</td>
<td>NMO</td>
<td>NMO</td>
<td>MS</td>
<td>MS</td>
<td>NMO</td>
<td>MS</td>
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<tr>
<td>Hypothalamic lesion</td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>REM abnormality</td>
<td>No data</td>
<td>SOREMPs</td>
<td>No data</td>
<td>SOREMPs</td>
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<td>No data</td>
<td>No data</td>
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</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>29</td>
<td>279</td>
<td>874d</td>
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<td>Optic neuritis</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Spinal cord lesion</td>
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<tr>
<td>Long spinal cord lesion</td>
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<td>-</td>
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<tr>
<td>AQP4 Ab</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Laboratory test and the initiation of treatment</td>
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<td></td>
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<td></td>
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<tr>
<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>2 d</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>3 wk</td>
<td>2 wk</td>
<td>2 d</td>
<td>8 d</td>
</tr>
<tr>
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<td>10 d</td>
<td>4 wk</td>
<td>5.5 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</td>
<td>present</td>
<td>treatment</td>
<td>No</td>
<td>3 wk</td>
<td>2-5 wk</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.

* Anti–human AQP4 Ab was measured at Niigata University.11

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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.
mune attack on AQP4, and this may secondarily affect the hypocretin neurons. Two additional NMO cases presenting with EDS with symmetrical hypothalamic lesions are also available, although neither anti–AQP4 antibody titer nor CSF hypocretin-1 level were measured in these cases.

However, our other 4 patients with MS with EDS and hypocretin deficiency were anti–AQP4 antibody negative at the time of blood testing (Table). Hypothalamic lesions were observed in only 3 patients among 89 who were diagnosed with NMO and 31 patients with high-risk NMO, and existence of sleep symptoms was not specifically described in these cases. It is possible that other antibody-mediated mechanisms are additionally responsible for the bilateral symmetric hypothalamic damage causing EDS in the patients with NMO/MS. Possibly, the 4 patients with MS whose anti–AQP4 antibody titers were negative could still have NMO, since anti–AQP4 antibody titer was tested only once for each subject during the course of the disease, and the assay was not standardized among the institutes. It is thus essential to further determine the immunological mechanisms that cause the bilateral hypothalamic lesions with hypocretin deficiency and EDS and their association with NMO and AQP4. This effort may lead to establishment of a new clinical entity, and the knowledge is essential to prevent and treat EDS associated with MS and its related disorders. None of our cases exhibited cataplexy, contrary to the 9 of 10 cases with symptomatic narcolepsy and MS reported in the past. Early therapeutic intervention with steroids and other immunosuppressants may thus prevent irreversible damage of hypocretin neurons and prevent chronic sleep-related symptoms.

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Author Contributions: Dr Kanbayashi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kanbayashi, Shimohata, Nishizawa, Shimizu, and Nishino. Acquisition of data: Nakamura and Nishino. Analysis and interpretation of data: Yaguchi, Yabe, and Nishino. Drafting of the manuscript: Kanbayashi, Shimizu, and Nishino. Critical revision of the manuscript for important intellectual content: Shimohata, Nakashima, Yaguchi, Yabe, Nishizawa, and Nishino. Administrative, technical, and material support: Shimohata and Nakashima. Study supervision: Shimohata, Nakashima, and Nishino.

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REFERENCES