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【 CASE REPORT 】

Somnolence Preceded the Development of a Subthalamic Lesion in Neuromyelitis Optica Spectrum Disorder

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Abstract:
A 67-year-old woman with neuromyelitis optica spectrum disorder (NMOSD) developed severe somnolence. Ten days after admission, fluid-attenuated inversion-recovery magnetic resonance imaging (MRI) revealed hyperintense areas around the bilateral hypothalamus, which were not present on MRI at admission. The orexin level, which is decreased in idiopathic narcolepsy, was slightly decreased in her cerebrospinal fluid. Immunosuppressive treatment and methylphenidate markedly improved her somnolence. This case shows that NMOSD in the acute phase can cause somnolence in a patient without apparent lesions in the hypothalamus.

Key words: neuromyelitis optica spectrum disorder, somnolence, orexin, hypothalamic lesion, modafinil, methylphenidate

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Introduction

Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune demyelinating diseases of the central nervous system. Somnolence occurs in rare cases of NMOSD as symptomatic narcolepsy, and is one of the diagnostic criteria described by Wingerchuk et al. (1). We herein report a case of NMOSD involving a patient who presented with severe somnolence and in which the appearance of hypothalamic lesions on magnetic resonance imaging (MRI) was delayed.

Case Report

A 67-year-old woman with a one-month history of somnolence was admitted to our hospital. She did not have an apparent family history of neurological disease. She had been admitted to our hospital one year previously due to consciousness disorder, and neuropsychiatric systematic lupus erythematosus (NPSLE) was suspected based on the findings of polyarthritis and anti-nuclear and anti-Smith antibody positivity; however, she did not fulfill the diagnostic criteria for NPSLE (2). There were no significant findings on brain MRI, with the exception of mild atrophy of the brain. Immunosuppressive therapy [1,000 mg of intravenous methylprednisolone (mPSL), daily for 5 consecutive days and 500 mg of intravenous cyclophosphamide, monthly for 5 consecutive months] showed remarkable effects and she fully recovered. During her present illness, one month prior to her admission, she presented with somnolence and consciousness disorder (Glasgow coma scale: E3V4M5). Her vital signs, including her percutaneous oxygen saturation (SpO_2) level (98% in room air), were stable. Serological examinations revealed anti-nuclear and anti-La/SSB antibody positivity and a Krebs von den Lungen (KL)-6 level of 1,226 U/mL. A cerebrospinal fluid (CSF) examination showed a mild increase in her protein level (59 mg/dL) with normal cell numbers and a normal glucose level. The level of CSF orexin (hypocretin), a hypothalamic neuropeptide that regulates arousal and sleep, was decreased (170 pg/mL; normal range 225-355 pg/mL). Fluid-attenuated inversion-recovery (FLAIR) magnetic resonance imaging (MRI) of the brain at admission revealed hyperintense areas (HIAs) around the left corpus striatum (Figure A-D). Electroen-

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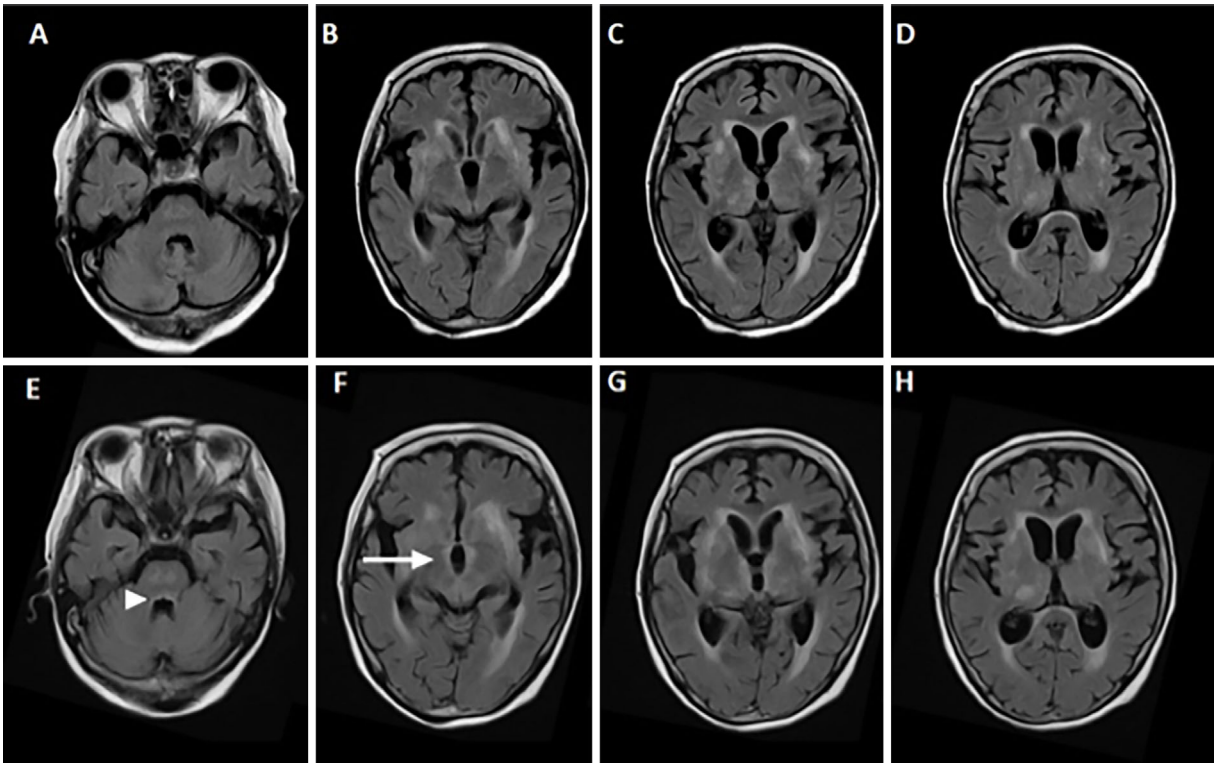

Figure. **Fluid-attenuated inversion recovery MRI before and after treatment. The upper part of the figure (A-D) shows hyperintense areas around the corpus striatum and periventricular region at admission. The lower part (E-H) shows new lesions appearing in the hypothalamus (F; arrow), periependymal region (E; arrowhead) and right thalamus (G and H) 10 days after admission, which were not observed at admission.**

cephalography revealed diffuse slow waves. Despite the administration of intravenous methylpredonisolone (mPSL) (IVMP; 1,000 mg/day) for 6 days, her somnolence did not improve. Furthermore, MRI at 10 days after admission revealed increased HIAs and new lesions in the hypothalamus, periependymal area and right thalamus (Figure E-H). Anti-aquaporin 4 (AQP4) antibody positivity [measured by enzyme-linked immunosorbent assay (ELISA)] and the presence of secondary narcolepsy led to a diagnosis of NMOSD based on the international consensus criteria (1). We concluded that the somnolence in this patient was caused by hypothalamic lesions. Immunoabsorption therapy (10 times) was added to her treatment regimen and a marked decrease in the HIAs was observed. We also initiated tacrolimus and per-oral prednisolone to prevent relapse. Although her total sleep time decreased after these treatments, she still slept for 20 hours a day. At 30 days after initiating IVMP treatment, modafinil was started, but even at 300 mg, she slept for 16 hours a day. At 80 days after initiating IVMP, we added methylphenidate (20 mg) and her sleeping time markedly decreased to 8 hours. At one month after starting methylphenidate, she presented with drug eruption and stopped taking methylphenidate. Her somnolence did not relapse and she was followed up as an outpatient.

Discussion

The present patient was diagnosed as NMOSD with somnolence related to a decreased orexin level. Hypothalamic lesions were detected on MRI approximately 40 days after the onset of symptoms, but not on admission. Orexin is a wake-promoting peptide and its level in the CSF is low in patients with idiopathic narcolepsy (3). A decreased orexin level in the CSF has also been reported in symptomatic narcolepsy associated with hypothalamic lesions, which is found in patients with many diseases including multiple sclerosis, tumor, acute disseminated encephalomyelitis, stroke, encephalitis, and NMOSD (4). Patients with symptomatic narcolepsy do not generally present with cataplexy or rapid eye movement sleep abnormalities, which are symptoms frequently observed in idiopathic narcolepsy. This patient did not fulfill the diagnostic criteria for idiopathic narcolepsy (5).

Interestingly, hypothalamic lesions were not found at the second admission, although our patient had already presented with somnolence. The appearance of visible spinal lesions in NMOSD patients may be delayed relative to the onset of clinical symptoms (6); however, whether the same delay occurs for intracranial lesions is unknown. It is difficult to conclude that the consciousness disorder that our patient presented with one year previously, was a symptom of

NMOSD. Unfortunately, anti-AQP4 antibody and CSF orexin were not examined at the time of the first admission. This case suggested that NMOSD might cause severe somnolence without apparent subthalamic lesions. It is important to determine whether orexin is decreased in the CSF, whether the patient is anti-AQP4 antibody-positive, and to repeat brain MRI to check for subthalamic lesions when clinicians examine patients with consciousness impairment of undetermined etiology.

There have been 15 reported cases of NMOSD in patients presenting with excessive sleep associated with hypothalamic lesions (7). To the best of our knowledge, this is the first case for which methylphenidate was used and in which an improvement of somnolence was observed in the acute phase of NMOSD. Methylphenidate, a noncompetitive dopamine and serotonin-noradrenaline reuptake inhibitor and secretagogue of dopamine, is a second-line treatment for idiopathic narcolepsy. There are two other cases for which modafinil was used to treat excessive sleep in NMOSD. One showed a marked recovery (7-9) but the other had a poor response (10). Brain MRI in the latter case showed atrophy of the hypothalamus, which was also found in our case (Figure). The wake-enhancing function of modafinil is mainly related to the blockade of the dopamine transporter (11). Although the function of modafinil is still unclear, modafinil might not improve somnolence associated with atrophy of the hypothalamus. In the 15 reported cases of somnolence in NMOSD patients with hypothalamic lesions, 12 of 13 cases were positive for anti-AQP4 antibody (the results of the anti-AQP4 antibody were not described in 2 out of 15 cases), and 7 of 12 cases recovered with prednisolone treatment. In almost all cases, pulse steroid therapy was effective for treating anti-AQP4-positive NMOSD. We added modafinil and methylphenidate because our patient still showed somnolence even after immunoabsorption therapy. One previous case reported the effect of modafinil and methylphenidate in secondary narcolepsy (12). A 11-year old boy in a vegetative state after the resection of astrocytoma and brain hemorrhage had extremely low brain levels of orexin. His symptoms were markedly improved by modafinil (200 mg) and methylphenidate (5 mg). Considering this report and our case, a combination of modafinil and methylphenidate might be a novel treatment for severe symptomatic narcolepsy.

Conclusions

In conclusion, we reported a unique case of NMOSD in which somnolence preceded a hypothalamic lesion on MRI. This case emphasizes the importance of checking and following brain MRI in patients with consciousness disorders, in order to distinguish NMOSD, even if subthalamic lesions are not observed on initial magnetic resonance images.

The Institutional Review Board of Juntendo Shizuoka Hospital approved this study.

Written informed consent for publication of this case report and any accompanying images were obtained from the patient.

The authors state that they have no Conflict of Interest (COI).

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