Neuromyelitis optica spectrum disorder with area postrema syndrome

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Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune inflammatory disorders associated with anti-aquaporin 4 (AQP4) antibodies.¹ The recent diagnostic criteria reflect the clinical variability of NMOSD and indicate that area postrema (AP) syndrome, acute brainstem syndrome, acute diencephalic syndrome, and symptomatic cerebral syndrome are core clinical entities in addition to optic neuritis and acute longitudinal myelitis.¹

Key clinical features that characterize AP syndrome include intractable hiccups and nausea/vomiting (IHNV), as well as lesions on the dorsal tegmentum of the medulla oblongata adjacent to the fourth ventricle visible through MRI.^{1,2} In this report, we describe a patient with NMOSD presenting AP syndrome accompanied with frequent syncope episodes coinciding with cardiac arrest.

PRACTICAL IMPLICATIONS

Cardiac arrest may be accompanied with intractable hiccups and nausea or appear independently in patients with neuromyelitis optica spectrum disorder.

Case

A 61-year-old woman was referred to our hospital because of frequent syncope events and persistent hiccups and nausea a year after a mastectomy and radiation therapy for breast cancer. A tamoxifen regimen served as maintenance therapy for complete remission. She began to experience nausea, vomiting, hiccups, and syncope episodes a week before hospital admission. The frequent events of syncope occurred independent of her posture.

Her primary doctor administered blood tests, an endoscopic examination, and an abdominal CT, but no abnormalities were detected. Neurologic examination on admission revealed no abnormalities. Electrocardiogram (EKG), EEG, and cardiac ultrasound results were normal. Head-up tilt test results for orthostatic hypotension (OH) were normal. However, Brain MRI showed a small lesion in the dorsal tegmentum of the medulla oblongata (figure, A–C). A cell-based assay was positive for serum anti-AQP4 antibodies. CSF examination revealed mild mononuclear pleocytosis (16/mm³) with a negative oligoclonal band. Holter EKG results elucidated recurrent events of cardiac asystole. EKG results revealed that cardiac asystole was induced immediately after hiccups or vomiting (figure, D). On admission, no drugs were administered that would predispose her to arrhythmia. The patient was diagnosed with NMOSD presenting AP syndrome. Her course of treatment was intravenous methylprednisolone pulse therapy (IVMP), with a dosage of 1 g/d for 3 days, followed by maintenance therapy with oral prednisolone. Her clinical symptoms disappeared completely within a week of commencing IVMP therapy.

Discussion

The AP, a sensory circumventricular organ located in the dorsal region of the midline medulla oblongata adjacent to the fourth ventricle, is characterized by a lack of tight junctions between

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Fluid-attenuated inversion recovery (FLAIR) imaging of a neuromyelitis optica spectrum disorder (NMOSD) lesion in the dorsal tegmentum of the medulla oblongata and cardiac asystole on an electrocardiogram (EKG) trace. The sagittal view (A) showing the lesion extending along the dorsal surface of the medulla oblongata (arrow head). The axial view (B: at the olivary nucleus level, C: at the obex level) showing the lesion in the dorsal tegmentum of the medulla oblongata including the area postrema and nucleus tractus solitarius (arrow heads). EKG results showing an appearance of asystole immediately after hiccup and vomiting (D).

vascular endothelial cells and the presence of fenestrated capillaries.^{3,4} These unique anatomical features facilitate not only blood stream monitoring but also the accessibility of anti-AQP4 antibodies. The AP also receives information from internal organs and has a pivotal role in regulating autonomic functions, including gastrointestinal and cardio-respiratory function, in association with nearby nuclei such as the nucleus tractus solitarius (NTS).^{3,4}

The dorsal medulla oblongata is one of the predilection sites in NMOSD and is implicated in IHN.² EKG monitoring revealed that cardiac asystole was triggered by hiccups and vomiting in our patient. This phenomenon may be caused by abnormal neural activation of the AP and NTS in the dorsal tegmentum of the medulla oblongata induced by an immune reaction mediating anti-AQP4 antibodies biased

toward parasympathetic system predominance.²⁻⁴ IHN caused in this condition may also stimulate gastric and respiratory mechanoreceptors resulting in sympathoinhibitory pathway activation involving vagal preganglionic neurons as a feedback mechanism.²⁻⁴

One report described a patient with NMOSD exhibiting IHN and OH as initial symptoms, followed by bulbar palsy and quadriparesis, presenting with a continuous lesion from the medulla oblongata to the upper cervical cord visible on MRI.⁵ Our patient showed a small lesion in the dorsal medulla but did not have OH. Thus, AP syndrome may have a diverse spectrum of symptom severity.

Our patient was not diagnosed with paraneoplastic neurologic syndrome (PNS) because PNS only refers to cases where

neurologic deficits are present before cancer development.⁶ However, a significantly high incidence of brainstem lesioning and IHN at onset have been reported in paraneoplastic NMOSD cases. Therefore, it is unclear whether the paraneoplastic mechanism was involved in the immunopathogenesis of our patient who developed NMOSD within 1 year of breast cancer resection.

Notably, NMOSD sometimes develops with AP syndrome as a sole manifestation at onset.⁷ Superfluous examinations such as endoscopy tests and abdominal CT scans might be performed for IHN, but with no results suggestive of NMOSD, the disorder might be overlooked. In addition, syncope and cardiac arrest may be other key features of AP syndrome. It is necessary to recognize AP syndrome quickly and accurately to commence therapy as early as possible because associated NMOSD recurrence correlates with devastating neurologic deficits.

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Appendix 1 Author contributions

Name	Location	Role	Contribution
Kazumasa Okada, MD, PhD	Occupational and Environmental Health School of Medicine, Kitakyushu, Japan	Author	Designed and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content
Masako Kobata, MD	Occupational and Environmental Health School of Medicine, Kitakyushu, Japan	Author	Major role in the acquisition of data
Satoshi Naruke, MD	Occupational and Environmental Health School of Medicine, Kitakyushu, Japan	Author	Major role in the acquisition of data

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