CASE REPORT

A Unique Shape of Brainstem Lesion that Caused Orthostatic Hypotension in Anti-NMDAR Encephalitis

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Abstract:

After experiencing upper respiratory-tract symptoms, a 41-year-old woman developed encephalitis with consciousness disturbance and respiratory failure. She had external ophthalmoplegia and facial diplegia. Magnetic resonance imaging revealed a brainstem lesion with spared longitudinal pontine bundles. Abnormal findings of the brainstem auditory-evoked potentials and blink reflex supported brainstem damage. The patient was positive for anti-N-methyl-D-aspartate receptor (NMDAR) antibodies. Repeated immunological treatments improved her symptoms, but severe orthostatic hypotension emerged. A head-up tilt test revealed no arginine vasopressin response to hypotension. The atypical symptoms of this case highlighted that the brainstem is one of the pivotal regions in anti-NMDAR encephalitis.

Key words: anti-NMDAR encephalitis, orthostatic hypotension, arginine vasopressin, magnetic resonance imaging, brainstem auditory-evoked potentials, blink reflex

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is characterized as an autoimmune-mediated limbic encephalitis presenting with peculiar neuropsychiatric manifestations (1). Autonomic symptoms, including respiratory and circulatory failure accompany the progression of the disease in most cases, and are included in the diagnostic criteria (2). The underlying pathophysiology is considered to be damage to the autonomic nervous center in the brainstem (3); however, there has been a lack of histopathological and neuroimaging evidence. We herein report a case of anti-NMDAR encephalitis presenting with cranial nerve disturbance and severe orthostatic hypotension due to a brainstem lesion demonstrated by magnetic resonance imaging (MRI), electrophysiological examinations, and a head-up tilt test.

Case Report

A 41-year-old woman who had previously been healthy and who had no problems in her daily life, presented with complaints of headache and fever after the onset of upper respiratory-tract symptoms, and was admitted to a city hospital. She transiently exhibited mild abnormal psychomotor symptoms followed by a gradual worsening of consciousness. Mechanical ventilation was needed due to the acute respiratory failure triggered by hypersalivation. She was then transferred to our hospital for further intensive care a week later. On examination, her general condition was normal, with the exception of an elevated body temperature (37.7°C). She received tracheal intubation and was on a mechanical ventilator. Her consciousness was impaired (Glasgow Coma Scale, E2VtM4). She had external ophthalmoplegia of the bilateral eyes and facial diplegia without lateral differences. No abnormal or involuntary movements were...
observed. Her deep tendon reflexes were exaggerated in the left arm and the plantar responses were bilaterally extensor. Laboratory tests revealed lymphocyte-dominant pleocytosis (52/μL), elevated protein (87 mg/dL), and a positive oligoclonal band in the cerebrospinal fluid (CSF). Cell-based assays revealed that both serum and CSF samples were positive for anti-NMDAR antibodies (4) but negative for anti-aquaporin 4 (AQP4), anti-myelin oligodendrocyte glycoprotein (MOG), and anti-ganglioside antibodies. No ovarian teratoma was noted. Brain MRI revealed an extensive brainstem lesion with cerebellar atrophy, with especially hyperintense signals in the central pons, with the exception of the longitudinal pontine bundles (Fig. 1A). Electroencephalography showed diffuse theta and delta waves but no paroxysmal spikes. The brainstem auditory-evoked potentials (BAEP) showed a prolonged interpeak interval between the third and fifth waves bilaterally, and the blink reflex was scantly evoked, suggesting damage to the brainstem (Fig. 1B and C). We diagnosed the patient with anti-NMDAR encephalitis.

The patient was treated with intravenous methylprednisolone pulse therapy (1 g over 3 days, administered five times), and intravenous immunoglobulin (0.4 g/kg over 5 days, administered twice). Her consciousness disturbance, ophthalmoplegia, and facial diplegia gradually and completely recovered. Follow-up MRI showed disappearance of the pontine hyperintensity but progression of the cerebellar atrophy (Fig. 1D). MRI revealed no abnormal findings in the supra-tentorial areas. The electrophysiological findings of the BAEP and blink reflex also improved (Fig. 1E and F). She continued to receive rehabilitation and became able to walk by herself; however, severe orthostatic hypotension and cerebellar ataxia emerged. The head-up tilt test produced an elevation of noradrenaline but no increase in arginine vasopressin (AVP) in response to induced hypotension (Fig. 2A-C). Subsequent activation of the renin-angiotensin aldosterone system may have compensated for the hypotension to maintain the blood pressure (Fig. 2D and E). She was treated with amezinium metilsulfate (oral) and droxidopa (oral), and was finally discharged from the hospital.

**Discussion**

Anti-NMDAR encephalitis classically presents with the following sequential symptoms: neuropsychiatric behavior and seizure involving the cortex, followed by movement disorders and autonomic symptoms related to dysfunction of
Figure 2. Results of the head-up tilt test. (A) Blood pressure in both the systolic and diastolic phases decreased dramatically by more than 60 mmHg and the pulse rate increased when the patient stood up. The blood pressure gradually recovered within 9 min after standing up. (B, C) An appropriate noradrenaline response was found but there was no release of arginine vasopressin. (D, E) Compensatory increases in renin and aldosterone levels led to recovery of the blood pressure. Gray areas show the normal ranges.

the basal ganglia and brainstem (5). The present patient showed atypical clinical features of consciousness disturbance, autonomic dysfunction, and facial diplegia, suggesting that the brainstem was preferentially affected but with no apparent association of the cortical lesions. The MRI findings supported our hypothesis regarding the localization of the lesions.

Almost half of the reported cases of anti-NMDAR encephalitis involve abnormal MRI findings in the medial temporal lobes and cerebral cortex; brainstem lesions have been extremely rare (1). Tüzün et al. reported a mild clinical case showing midbrain lesions but no findings in the cortex (6). The present patient showed a uniquely shaped brainstem lesion that preserved the longitudinal pontine bundles bilaterally, indicating that her cranial nerve symptoms were related to damage to the transversal fibers and nuclei. There has been a previous case report of a case in which brainstem involvement was suspected from clinical signs such as hypventilation with abnormal eye movement (7); however, no previous study confirmed brainstem dysfunction by electrophysiological testing, as was performed in the present case. To the best of our knowledge, this is the first confirmed case of anti-NMDAR encephalitis in which the brainstem lesion was chronologically followed using electrophysiological methods.

AVP and noradrenaline are associated with the arterial baroreflex, and the measurement of the serum levels of these hormones is helpful for detecting lesions causing orthostatic hypotension (8). The present case did not exhibit increased AVP release while standing, whereas the patient’s noradrenaline level rapidly increased from the normal level when she stood up. These observations suggested the function of the baroreceptor and sympathetic nervous systems was normal, but also indicated the impairment of the central afferent pathways from the vasomotor center in the medulla oblongata to the hypothalamus, which was supported by the MRI findings.

It has been known that other autoantibodies (e.g., anti-AQP4, anti-MOG, and anti-ganglioside antibodies) are concomitantly detected in anti-NMDAR encephalitis patients
with unusual clinical episodes (9, 10). These antibodies were not detected in the present case; however, unknown autoantibodies might have been associated with the pathophysiology of the atypical clinical features in the present case.

Our patient showed atypical clinical signs that were related to the brainstem lesion, as revealed by unique MRI and electrophysiological findings. The loss of AVP release with a normal noradrenaline response when standing up also supported this assumption. The brainstem should therefore be considered as a key target of anti-NMDAR encephalitis in patients who present with various unusual clinical features.

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

Ethics Statement
Written informed consent was obtained from the patient for the publication of this case report.

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Author contributions
T. Murakami managed the patient and wrote the first draft of the manuscript. S. Nakatani-Enomoto and H. Enomoto managed the patient and revised the manuscript. Y. Takahashi measured the antibodies and revised the manuscript. Y. Ugawa revised the manuscript and provided intellectual content.

References

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