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 developed 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. Neither abnormal nor involuntary movements

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ophthalmoplegia, and facial diplegia gradually and com-
days, administered twice). Her consciousness disturbance,
times), and intravenous immunoglobulin (0.4 g/kg over 5
long pulsed therapy (1 g over 3 days, administered five
sample with anti-NMDAR encephalitis.
ling damage to the brainstem (Fig. 1B and C). We diagnosed
bilaterally, and the blink reflex was scantly evoked, suggest-
diffuse theta and delta waves but no paroxysmal spikes. The
brainstem auditory-evoked potentials (BAEP) showed a pro-
tentration of the cerebellum preserving the longitudinal
brainstem lesion with cerebellar atrophy, with especially hyperin-
tumor was noted. Brain MRI revealed an extensive brain-
tein (MOG), and anti-ganglioside antibodies. No ovarian
assays revealed that both serum and CSF samples were posi-
cytosis (52/μL), elevated protein (87 mg/dL), and a positive
in the left arm and the plantar responses were bilaterally ex-
were observed. Her deep tendon reflexes were exaggerated
in the left arm and the plantar responses were bilaterally ex-
tensor. Laboratory tests revealed lymphocyte-dominant pleo-
cytosis (52/μL), elevated protein (87 mg/dL), and a positive
upestasis in the central pons preserving the longitudinal
s were observed. Her deep tendon reflexes were exaggerated
ntry in the central pons along with spared longitudinal pontine bundles. Diffuse
atrophy of the cerebellum and enlargement of the fourth ventricle were noted. (B) The brainstem
auditory evoked potentials (BAEPs) reveal that the interpeak intervals were prolonged between the
and fifth waves. (C) Delays of R1 and poor R2 responses were shown in the blink reflex. One and
a half years later, (D) T2WI showed the improvement of hyperintensity in the central pons with pro-
gression of the cerebellar atrophy. (E, F) The BAEP and blink reflex findings normalized.

Figure 1. Brain magnetic resonance imaging and electrophysiological examinations. One month
after consciousness disturbance, (A) A T2-weighted image (T2WI) shows an area of high signal inten-
sity with a unique shape in the central pons along with spared longitudinal pontine bundles. Diffuse
atrophy of the cerebellum and enlargement of the fourth ventricle were noted. (B) The brainstem
auditory evoked potentials (BAEPs) reveal that the interpeak intervals were prolonged between the
third and fifth waves. (C) Delays of R1 and poor R2 responses were shown in the blink reflex. One and
a half years later, (D) T2WI showed the improvement of hyperintensity in the central pons with pro-
gression of the cerebellar atrophy. (E, F) The BAEP and blink reflex findings normalized.

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in the left arm and the plantar responses were bilaterally ex-
tensor. Laboratory tests revealed lymphocyte-dominant pleo-
cytosis (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 posi-
tive for anti-NMDAR antibodies (4) but negative for anti-
aquaporin 4 (AQP4), anti-myelin oligodendrocyte glycopro-
tin (MOG), and anti-ganglioside antibodies. No ovarian
teratoma was noted. Brain MRI revealed an extensive brain-
stem lesion with cerebellar atrophy, with especially hyperin-
tense signals in the central pons preserving the longitudinal
pons bundles (Fig. 1A). Electroencephalography showed
diffuse theta and delta waves but no paroxysmal spikes. The
brainstem auditory-evoked potentials (BAEP) showed a pro-
longed interpeak interval between the third and fifth waves
bilaterally, and the blink reflex was scantly evoked, suggest-
ing damage to the brainstem (Fig. 1B and C). We diagnosed
the patient with anti-NMDAR encephalitis.

The patient was treated with intravenous methylprednis-
lone 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 com-
pletely 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 induced an elevation of noradrenaline but no increase in
arginine vasopressin (AVP) in response to hypotension
(Fig. 2A-C). Subsequent activation of the renin-angiotensin
aldosterone system may have compensated for the hypoten-
sion to maintain the blood pressure (Fig. 2D and E). She
was treated with amezinium metilsulfate (oral) and droxi-
dopa (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 dis-
orders and autonomic symptoms related to dysfunction of
the basal ganglia and brainstem (5). The present patient
showed atypical clinical features of consciousness distur-
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.

Figure 2.

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 autoanti-
bodies 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.

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

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

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