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QUIZ CASES

Neuromyelitis optica spectrum disorders with multiple brainstem manifestations: a case report

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Abstract
Background Multiple brainstem manifestations have been rarely reported during the same attack in neuromyelitis optica spectrum disorders (NMOSD).
Case presentation We describe a 39-year-old Asian woman presenting multiple brainstem manifestations including intractable nausea and vomiting, vertigo, diplopia, facial palsy, hypogeusia, ophthalmoplegia, hemiplegia, dysphagia and tonic spasm during the same attack. Hypogeusia was transient and recovered without any immunotherapy. The brain MRIs showed progressive multiple lesions in the brainstem. NMO-IgG (aquaporin4-antibody, AQP4-Ab) were positive in both serum and cerebral spinal fluid. The symptoms and signs were controlled after immunosuppressive therapy. No relapse happened during the 15-month follow-up.
Conclusion This report emphasizes multiple brainstem manifestations during the same attack in NMOSD and the most characteristic symptom was reversible hypogeusia.

Keywords Multiple brainstem manifestations · Transient hypogeusia · Neuromyelitis optica spectrum disorders

Abbreviations

NMOSD	Neuromyelitis optica
MRI	Magnetic resonance imaging
CSF	Cerebral spinal fluid
AQP-4	Aquaporin 4
AQP4-Ab	Aquaporin 4 antibody
VEP	Visual evoke potential
ON	Optic nerve
LEM	Longitudinally extensive myelitis
ELISA	Enzyme linked immunosorbent assay
NTS	Nucleus tractus solitaries
INH	Intractable nausea and vomiting
MO	Medulla oblongata

Introduction

Neuromyelitis optica (NMO) is a severe demyelinating disorder characterized by spinal cord and optic nerve (ON) involvement, causing mainly recurrent blindness and paralysis [1]. The serum autoantibody, NMO-IgG, binding to water channel protein aquaporin 4 (AQP-4) had been reported as a biomarker of NMO [2, 3]. The discovery of NMO-IgG had also prompted a new term of NMOSD including a proportion of patients with recurrent, isolated, longitudinally extensive myelitis (LEM) or ON, as well as patients with LEM or ON associated with systemic autoimmune disease or with brain lesions typical of NMO [4]. Recently, numerous studies have reported abnormalities in the brain MRIs of NMOSD patients. The incidences of brain abnormalities range from 50 to 85 % [5]. A multicenter study showed brainstem abnormalities in 81 (31.4 %) of 258 patients with NMOSD. The most common clinical manifestations were vomiting (33.1 %), hiccups, oculomotor dysfunction (19.8 %), pruritus, followed by hearing loss, facial palsy (2.5 %), vertigo or vestibular ataxia (1.7 %), trigeminal neuralgia and other cranial nerve

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signs (3.3 %). Only 16 patients (6.2 %) had two or more brainstem symptoms during the same attack [6].

Here, we presented a case of NMOSD with multiple brainstem symptoms including intractable nausea and vomiting, vertigo, diplopia, facial palsy, hypogeusia, ophthalmoplegia, hemiplegia, dysphagia and tonic spasm during the same attack, especially hypogeusia recovering without immunotherapy.

Case report

A 39-year-old Asian woman with a 10-year history of hyperthyroidism presented intractable nausea and vomiting after a flu-like illness. One month later, she developed vertigo. She received the evaluations of general physician and gastroenterologist without any abnormal findings. All of the above symptoms continued for 2 months prior to admission to our hospital. Neurological examination only disclosed bilateral horizontal nystagmus. Routine laboratory investigations including blood routine tests,hepatic and renal functions,electrolyte, glucose, lipids, inflammatory markers, erythrocyte sedimentation rate and coagulation function were normal. Microbiological and autoimmune antibodies' tests were normal except for elevated thyroid relevant antibody (Table 1).

Brain MRI was performed (Fig. 1a). Marked signal abnormalities were noted in the bilateral dorsal medulla with low-intensity signal on T1-weighted images, high-intensity signal on T2-weighted and diffusion weighted images. But, there was no enhancement after administration of gadolinium–diethylenetriamine pentaacetic acid contrast material. Wernicke′s encephalopathy, acute disseminated encephalomyelitis and optico-spinal MS were suspected.

However, antiemetic and intravenous nutrition treatment was ineffective. Furthermore, hypogeusia, diplopia, numbness on the right face and left peripheral facial paralysis appeared 1 week after admission. The detailed examination showed diminished sense of four fundamental tastes in entire right side and anterior left side of the tongue, limited left eye outreach and diminished sensation to pinprick on the right face. Repeated brain MRIs showed the enlarged lesions spreading to the pons and cerebellar peduncles (Fig. 1B). At the same time, vertigo, nausea and vomiting aggravated (Table 2). However, CSF examination showed normal cell count, total protein and electrolyte. The oligoclonal bands were negative. For confirming the diagnosis, blood and CSF test were done to look for AQP4-Ab status by enzyme linked immunosorbent assay (ELISA). Dramatically, nausea, vomiting and gustation remitted gradually and recovered during the 2 weeks waiting for the results. Repeated brain MRIs (Fig. 1c, d) still revealed the progressive enlargement of the lesions in the brainstem. AQP4-antibodies were strongly positive (+++) in both the serum and CSF. The patient did not accept the test of AQP4 titer considering economy. Therefore, acute disseminated encephalomyelitis and optico-spinal MS were denied and a diagnosis of NMOSD was made. Furthermore, visual evoked potential (VEP) and spinal MRIs were normal.

Then, the patient received intravenously methylprednisolone (1000 mg/day for 3 days, 500 mg/day for 3 days, 250 mg/day for 3 days) initially and immunoglobulin (0.4 g/kg for 5 days) subsequently. But she presented dysphagia, limited horizontal movement of eyes and left limb weakness with grade 4 out of 5, 3 days after immunosuppressive therapy. Vertigo and diplopia also aggravated (Table 2). Repeated brain MRIs showed further enlargement of lesions (Fig. 1e). We detected AQP4-Ab again and the result showed positive, but not strongly like before (++). Luckily, in the days ahead, she started to respond to the treatment. All of the above symptoms disappeared except for vertigo and diplopia 2 weeks later (Table 2). The brain MRIs were performed again and the lesions did not show obvious enlargement (Fig. 1f). Two days after finishing the intravenous treatment, she felt tonic spasm of her left limb, and it was controlled by oral carbamazepine for 5 days. The patient was discharged and the treatment of oral methylprednisolone and azathioprine continued.

Three months after discharge, the reviewed brain MRI showed obvious resolution of the lesions (Fig. 1g). There was no enhancement in all of the above MRIs. At 15-month follow-up, she kept taking azathioprine orally and only felt dizzy mildly at times.

Table 1 Abnormal results of immunological investigations

Immunology	Patient	Normal range
ATPO (thyroid peroxidase antibody)	60.7 U/ML	0–60 U/ML
ATG (thyroglobulin antibody)	139.0 U/ML	0–60 U/ML
TRAb (TSH receptor antibody)	3.49 U/L	0–1.75 U/L

Discussion

Various brainstem symptoms such as intractable hiccups, nausea and vomiting, nystagmus, dysarthria, dysphagia, ataxia, or ophthalmoplegia were very common in NMO/NMOSD [5]. There were also some rare manifestations like hearing loss, facial palsy, vertigo or vestibular ataxia, trigeminal neuralgia, hypogeusia and other cranial nerve signs [6–8].

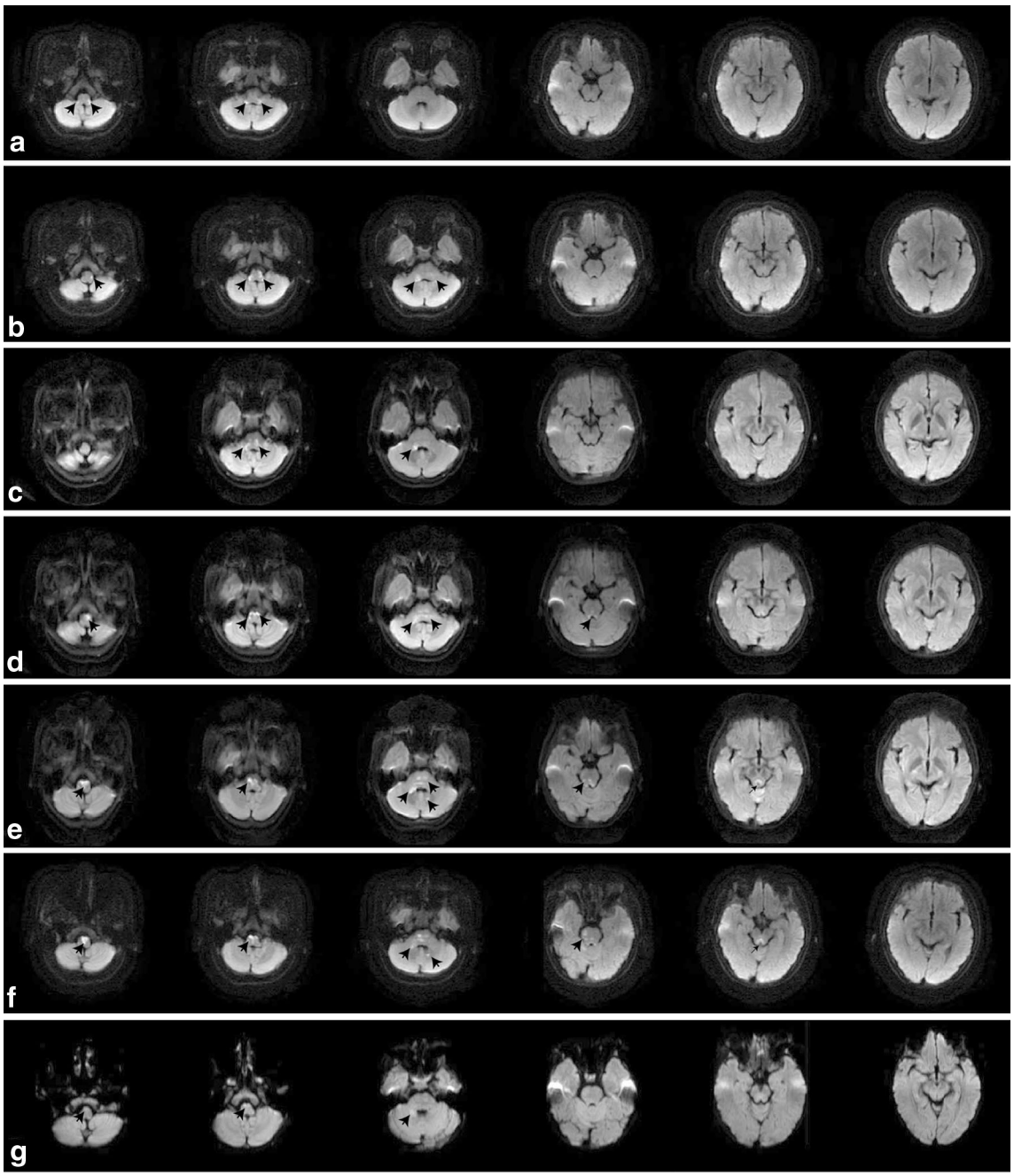

Fig. 1 Magnetic resonance imaging of the brain. One day after admission to hospital, **a** diffusion weighted imaging transverse image shows bilateral dorsal medullary lesions of high-intensity signal. One-week intervals after admission **b**, **c**, **d** the lesions enlarged gradually in the brainstem. Three days after immunosuppressive therapy **e** the lesions enlarged continuously. The immunosuppressive therapy was finished **f** the lesions did not enlarge obviously. Three months after discharge **g** the lesions showed obvious resolution. The *arrows* indicate the lesions

Clinical features of our patient are characterized by multiple dysfunctions of brainstem, manifesting as intractable nausea and vomiting, vertigo, diplopia, facial palsy, transient hypogeusia, ophthalmoplegia, hemiplegia, dysphagia and tonic spasm in the same course. Brain MRI revealed multiple progressive lesions in the brainstem. Spinal cord MRIs and VEP were negative. AQP4-antibodies were detected in both serum and CSF. A diagnosis of NMOSD was made.

Hypogeusia was rarely reported in NMO/NMOSD [7, 8]. Knowledge on human central taste pathways is mostly based on anatomical data. Peripheral gustatory fibres are

Table 2 Symptoms and signs in the disease course

Symptoms and signs	2 months before admission	1 month before admission	1 day after admission	1 week after admission	2 weeks after admission	3 weeks after admission	3 days after immunotherapy	Immunotherapy finished	2 days after treatment
Images (Fig. 1)	NA	NA	Fig. 1a	Fig. 1b	Fig. 1c	Fig. 1d	Fig. 1e	Fig. 1f	NA
Nausea and vomiting	+++	+++	+++	++	+	−	−	−	−
Vertigo	−	+++	+++	++	++	++	+++	+	+
Diplopia	−	−	−	++	++	++	+++	+	+
Left facial palsy	−	−	−	+	+	+	+	−	−
Hypogeusia	−	−	−	+++	++	−	−	−	−
Right facial hypaethesia	−	−	−	++	++	++	++	−	−
Left ophthalmoplegia	−	−	−	+	+	+	+	−	−
Right ophthalmoplegia	−	−	−	−	−	−	+	−	−
Left hemiplegia	−	−	−	−	−	−	+	−	−
Dysphagia	−	−	−	−	−	−	+	−	−
Tonic spasm	−	−	−	−	−	−	−	−	++

NA, not applicable; +++, severe; ++, moderate; +, mild

carried within cranial nerves VII, IX, and X, and converge to the nucleus tractus solitarius (NTS) in the medulla. Second order fibres ascend ipsilaterally from the NTS towards the tegmentum of pons and they reach the thalamic gustatory nucleus. As for our patient, the involvement of bilateral NTS and tegmentum seen in MRIs might be the cause.

The reason why it recovered without treatment was unknown. However, the reversibility of intractable vomiting had been suggested to be the consequence of loss of AQP-4 and inflammation in the medullary floor of the fourth ventricle including the area postrema. The results were different from the necrosis lesions [9]. Therefore, transient hypogeusia does not seem to be surprising when taking into account ongoing dynamic inflammatory processes. Besides, under normal circumstances, efficient remyelination can lead to complete repair with functional recovery [10].

Tonic spasm is paroxysmal tonic muscle contraction affecting left limbs lasting less than one minute and is a common clinical manifestation in NMO. The mechanism is perhaps axonal activation secondary to ephaptic cross-transmission in the demyelinated plaques at any level of the motor path. It can be controlled by carbamazepine [11].

Intractable nausea and vomiting (INH) have been reported as a herald exacerbation and were often preceded by an episode of viral infection [12], which is consistent with our patient. These manifestations are thought to be due to vulnerability within the area postrema to serological factors such as AQP4-Ab [13, 14].

Dysphagia is a relative common type of presentation in NMOSDs and was found in 29.5 % of NMOSDs patients with medulla oblongata (MO) lesions [15]. The neural network in relation to nucleus ambiguus, NTS, and dorsal vagal nuclei in MO may be responsible for this manifestation.

The correlation between AQP4-Ab serum levels and clinical disease activity had been confirmed. The titres were preceded by an up to 3-fold in relapse [16]. Although our patient has not relapsed in her course of disease, the serum AQP4-Ab absorbance decreased when she accepted the immunosuppressive therapy. Recently, Yanqiang Wang et al. reported that NMOSD patients with MO lesions were more frequently complicated with thyroid disease [15], which is absolutely accordant to our patient.

In conclusion, our case presented multiple brainstem manifestations including intractable nausea and vomiting, vertigo, diplopia, facial palsy, transient hypogeusia, ophthalmoplegia, hemiplegia, dysphagia and tonic spasm during the same attack. An understanding of diverse brainstem manifestations is crucial for early and correct diagnosis of NMOSD.

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Conflict of interest The authors declare that there are no conflicts of interest.

Informed consent Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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