Multiple Sclerosis and Related Disorders 35 (2019) 185–192

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Case report

AQP4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD) coexisting with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: A case report and literature review

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ARTICLE INFO

Keywords:
Neuromyelitis optica spectrum disorder (NMOSD)
aquaporin 4 immunoglobulin G (AQP4-IgG)
Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis
NMDAR antibodies

ABSTRACT

Background: Neuromyelitis optica spectrum disorder (NMOSD) can coexist with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Patients with overlapping Aquaporin 4 immunoglobulin G (AQP4-IgG)-seropositive NMOSD and anti-NMDAR encephalitis with positive NMDAR antibodies in the cerebrospinal fluid (CSF) are rare but should not be ignored.

Methods: A unique case of NMOSD coexisting with anti-NMDAR encephalitis is presented. Case reports of AQP4-IgG-seropositive NMOSD overlapping with anti-NMDAR encephalitis with positive NMDAR antibodies in the CSF were reviewed.

Results: A 61-year-old female presented with headache, blurred vision, dysuria, limb weakness, coma, respiratory failure, and hypotension. Brain magnetic resonance imaging (MRI) showed abnormal signals in the left temporal lobe, white matter around the bilateral ventricles, midbrain, medulla oblongata, cervical, and upper thoracic medulla. AQP4-IgG antibodies were positive in the serum and CSF. NMDAR antibodies were positive in the CSF. The patient's condition was stable following intravenous gamma globulin, corticosteroids, immunosuppressants, and symptomatic support treatments. Only a single met the criteria of NMOSD simultaneously coexisting with anti-NMDAR encephalitis in addition to our own case.

Conclusions: This case provides further evidence for the occurrence of NMOSD with AQP4-IgG-seropositive overlapping anti-NMDAR encephalitis in a Chinese patient. The mechanisms underlying the occurrence of double positive antibodies remains elusive. When NMOSD patients show unusual symptoms (abnormal behavior, prominent psychiatric manifestations, cognitive dysfunction, autonomic dysfunction), or atypical supratentorial lesions, the coexistence of anti-NMDAR encephalitis should be considered.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a spectrum of humoral immunity that involves antigen-antibody mediated inflammatory demyelinating disease in the central nervous system (CNS). The main diagnostic basis of NMOSD is serum aquaporin 4 immunoglobulin G (AQP4-IgG) antibodies and 6 core clinical symptoms that include optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome, and symptomatic cerebral syndrome (Wingerchuk et al., 2015). Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common type of autoimmune encephalitis, the six major symptoms of which include abnormal behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorders or dyskinesias or abnormal posture, decreased consciousness, and autonomic dysfunction or central hypoventilation (Graus et al., 2016).

AQP4-IgG-seropositive patients with NMOSD often coexist with autoimmune disorders, including Sjögren syndrome, systemic lupus erythematosus, hashimoto's disease, and myasthenia gravis. Patients with anti-NMDAR encephalitis develop concurrent or separate episodes

Abbreviations: AQP4-IgG, aquaporin 4 immunoglobulin G; CBA, cell-based assays; CNS, central nervous system; CSF, cerebrospinal fluid; DSE, demyelination syndrome episode; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone pulse; LETM, longitudinally extensive transverse myelitis; MOG-ab, myelin oligodendrocyte glycoprotein-antibody; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NMOSD, Neuromyelitis optica spectrum disorder; NMDAR, N-methyl-D-aspartate receptor

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https://doi.org/10.1016/j.msard.2019.07.008
Received 13 May 2019; Accepted 19 July 2019

of demyelinating disorders (Titulaer et al., 2014). The co-morbidity of NMOSD and anti-NMDAR encephalitis are less frequently reported.

2. Methods

A unique case of AQP4-IgG-seropositive NMOSD coexisting with anti-NMDAR encephalitis with positive NMDAR antibodies in the CSF was reported. To review the relevant literature, the PubMed database was searched using the terms: ('Neuromyelitis Optica' OR 'Neuromyelitis optica spectrum disorder') AND ('Receptors, N-Methyl-D-Aspartate' OR 'Anti-N-Methyl-D-Aspartate Receptor Encephalitis'). The reference lists of all included studies were also screened. Searches were performed up to February 2019. According to the diagnostic criteria for NMOSD with AQP4-IgG proposed by Wingerchuk et al. (2015), and the diagnostic criteria for definite anti-NMDAR encephalitis defined by Graus et al. (2016), the diagnosis can be made in the presence of one or more of the clinical symptoms and corresponding antibody positivity.

3. Results

3.1. Case presentation

A 61-year-old female Han Chinese patient showed symptoms of headache and blurred vision for 12 days, dysuria for 9 days, and weakness of the limbs for 6 days. She was admitted to the Xuanwu Hospital of Capital Medical University on February 24, 2018. Six months ago (August 24, 2017), she was hospitalized in another hospital with numbness of the left limb and speech difficulties for 3 days. On the third day of hospitalization, the patient had sudden bosom frowsty, difficulty breathing, and blood gas analysis suggested type I respiratory failure. Mechanical ventilation was used to help the patients breathing. During the hospitalization on September 7, 2017, brain magnetic resonance imaging (MRI) showed T2 hyperintense signals within the medulla oblongata. After therapy, the patient was taken offline and left the hospital with dysphagia and numbness of the left limb after discharge, requiring nasal feeding. Twelve days prior to admission, the patient presented with headache, mainly in the left temporal occipital region, with paroxysmal swelling pain accompanied by blurred vision in both eyes, particularly the left eye. Nine day prior to admission, the patient experienced dysuria, and urine and stool retention. Six days before admission, the patient experienced limb weakness and was treated with a single course of intravenous immunoglobulin (IVIG, 20g, 0.4 g/kg) in another hospital. Neurology examinations in the hospital at this time noted lethargy, dysphasia, bilateral optic neuritis, and acute myelitis. The primary diagnosis was neuromyelitis optica. Brain MRI (February 20, 2018) showed multiple hyperintense T2 lesions and T2-weighted fluid-attenuated inversion recovery (FLAIR) lesions within the medulla oblongata and left temporal pole (Fig. 1 a–c).

Following admission, the disease rapidly progressed, and the disturbance of consciousness changed from lethargy to coma. Blood pressure decreased and vasoactive drugs were administered to maintain blood pressure. Respiratory failure occurred, so tracheal intubation and mechanical ventilation were used to assist breathing. Refractory hyponatremia occurred and continuous sodium supplementation was provided. Following lumbar puncture examination, the pressure exceeded 350 mmH_2O, and CSF analysis showed a total cell count of 416×10^6/L, a white blood cell count of 216×10^6/L, and modestly increased protein concentrations (56 mg/dl). The serum and CSF were tested for AQP4-IgG by indirect immunofluorescence and cell-based assays (CBA), showing positivity in both assays. Autoimmune encephalitis antibodies were further examined and NMDAR antibodies were positive in the CSF and negative in the serum. CASPR2, AMPAR, LGI1, GABAB and DPPX antibodies were all negative. Tests for classical onconeural antibodies (Hu, Ri, Yo, Ma2, CV2/CMRP5, amphiphysin) were negative. Antiglycolipid antibodies (GM1, GD1b, GQ1b) were negative. Antinuclear antibodies (ANA), anti-neutrophilcytoplasmic antibodies (ANCA), anti-Sjögren syndrome A (SSA) antibody and anti-Sjögren syndrome B (SSB) antibodies were also negative. After admission, we treated the patient with IVIG (20 g, 0.4 g/kg, per day for 5 days) and intravenous methylprednisolone pulse (IVMP, 1 g per day for 5 days) which was gradually tapered. Following IVMP therapy, oral prednisone and mycophenolate mofetil (250 mg bid for 3 days, up to 500 mg bid) were administered. During disease progression, complications including bacterial pneumonia, anemia, acute gastric mucosal lesions and bleeding, hypoproteinemia, abnormal liver function, electrolyte disorders, and an imbalance of intestinal flora occurred, so symptomatic support therapy was provided. One week after admission, the patient could open her eyes autonomously and had a sleep wake cycle that was considered akinetic mutism. In the second month after admission, there was nystagmus, visual object tracking, mouth opening, and other involuntary movements of the tongue. Serum AQP4 and CSF NMDAR antibodies were positive on 3 occasions during disease progression. Two weeks after admission (March 6, 2018), the patient showed nerve lesions around the limbs with the involvement of motor fibers diagnosed through electromyography detection. One month after admission, a pattern of increasing slow waves was shown by electroencephalogram (EEG). Six weeks after admission (April 12, 2018), brain and spinal cord MRIs showed multiple T2-weighted and T2-weighted FLAIR hyperintense signals in the left temporal lobe, white matter around the bilateral ventricles, midbrain, medulla oblongata, cervical, and upper thoracic medulla in the absence of gadolinium enhancement (Fig. 1 d–l).

Following immune therapy, life support, and symptomatic treatment, the patient's vital signs were stable 2 months after admission. She was transferred to the local hospital for further rehabilitation. Following hospital release, akinetic mutism, independent eye opening, visual object tracking, and involuntary movements such as tongue extension, mouth opening, occasional tremors of both hands and thumbs, limb muscle strength level 0, a loss of tendon reflexes, and bilateral pathological signs were negative. The patient was followed up and died of pulmonary infection 3 months after leaving hospital.

3.2. Literature review

In view of the specificity of positive antibodies in the diagnostic criteria, references on the case reports of AQP4-IgG-seropositive NMOSD overlapping with anti-NMDAR encephalitis with positive NMDAR antibodies in the CSF were reviewed. Previous cases including the demographics, clinical features, and neuroimaging findings are summarized in Tables 1 and 2. Based on the diagnostic formula, we found only a single case that met the criteria of NMOSD simultaneously coexisting with anti-NMDAR encephalitis in addition to our own case (Table 1) (Fan et al., 2018). Watanabe et al. (2014) reported a case that was associated with anti-NMDAR encephalitis during the third recurrence of NMOSD, however, NMDAR antibodies were positive in the serum and the CSF was not examined. Qin et al. (2017) reported 4 cases of atypical anti-NMDAR encephalitis, 1 of which was double positive for serum AQP4-IgG and CSF NMDAR. However, the patient had no major symptoms of anti-NMDAR encephalitis from the diagnostic criteria.

Table 2 describes five patients who presented with AQP4-IgG-seropositive NMOSD at onset followed by anti-NMDAR encephalitis. Titulaer et al. (2014) focused on anti-NMDAR encephalitis coexisting with demyelinating disorders. Amongst 691 patients with anti-NMDAR encephalitis, 9 showed combined AQP4-IgG-seropositivity and NMDAR antibodies in the CSF. Four of these patients had independent episodes of NMOSD (Table 2). The other 5 patients showed symptoms compatible with demyelination through MRI. A single patient was double positive in a control group of 50 randomly selected patients with typical anti-NMDAR encephalitis, but no clinical manifestations of NMOSD were observed. Luo et al. (2016) reported a young woman who initially

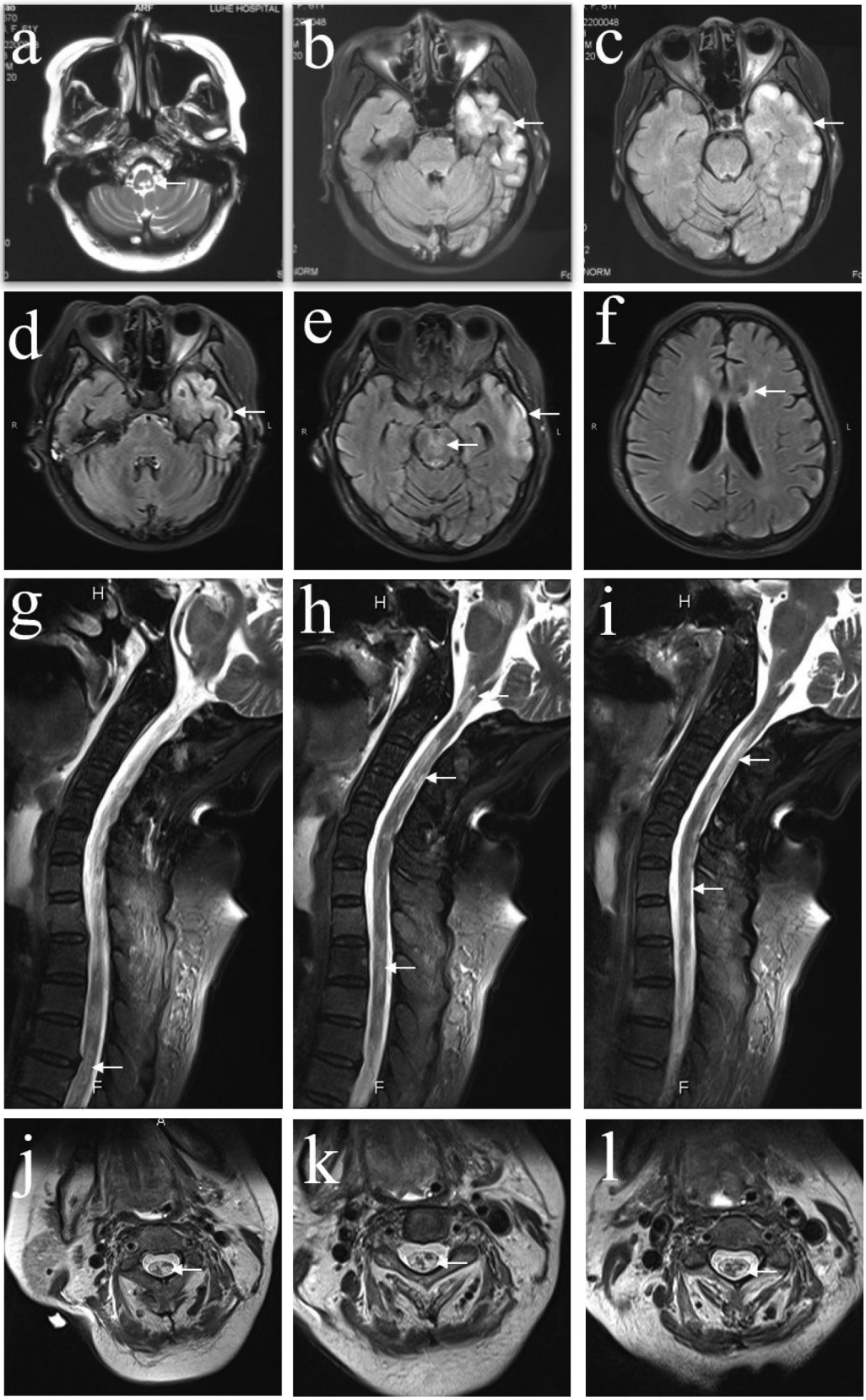

Fig. 1. Brain and spinal cord MRIs of the patient. Four days prior to admission, T2-weighted and T2-weighted FLAIR MRI showed abnormal hyperintense signals in the medulla oblongata (a) and the left temporal pole (b and c). Six weeks after admission, T2-weighted FLAIR and T2-weighted MRI showed multiple hyperintense lesions within the left temporal lobe (d and e), midbrain (e), white matter around the bilateral lateral ventricles (f), medulla oblongata, cervical medulla and upper thoracic medulla (g–l)

Table 1
Clinical features of two patients with AQP4-IgG-seropositivity with NMOSD simultaneously coexisting with anti-NMDAR encephalitis.

Source	Sex/Age at onset, y	Clinical characters of NMOSD	Clinical characters of anti-NMDAR encephalitis	MRI findings	AQP4-IgG-ab (dilution), CSF/ Serum	NMDAR-ab (dilution),CSF/ Serum	Immune therapy	mRS max	Last mRS
Case presented in this article.	F/61	Optic neuritis, acute myelitis with LETM, refractory hyponatremia.	Decreased consciousness, mutism, involuntary movements such as mouth opening and tongue extensions.	Multiple T2-weighted and T2-weighted FLAIR hyperintense signals in the left temporal lobe, white matter around the bilateral ventricles, midbrain, medulla oblongata, cervical and upper thoracic medulla.	Positive (1:100)/ positive (1:100)	Positive (1:100)/ negative	IVIG, IVMP, MMF	5	6
Fan et al.	F/62	Acute myelitis.	Lethargy, verbal loss, abnormal behavior, central hypoventilation, mutism.	T2 hyperintense lesions in the left periventricular white matter, bilateral frontal lobes, hypothalamus, and left thalamus, with partial enhancement.	Positive (1:1)/ Positive (1:32)	Positive (1:100)/ negative	IVMP, IVIG, MMF	5	4

ab = antibodies; AQP4-IgG = Aquaporin 4 immunoglobulin G; CSF = cerebrospinal fluid; F = female; FLAIR = fluid-attenuated inversion recovery; IVIG = intravenous immunoglobulins; IVMP = intravenous methylprednisolone; LETM = longitudinally extensive transverse myelitis; max = maximum; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; mRS = modified Rankin scale; NMDAR = N-methyl-D-aspartate receptor; NMOSD = neuromyelitis optica spectrum disorder; y = year.

presented with a diencephalic syndrome with AQP4-IgG. She was diagnosed with NMOSD, developed cognitive impairment, psychiatric symptoms, and dyskinesia ten months later. She was positive for serum-AQP4-IgG and CSF-NMDAR.

Tables 2 also describes four patients who presented with anti-NMDAR encephalitis at onset who were followed by NMOSD. Zoccarato et al. (2013) reported a 50-year-old female patient who developed limbic encephalitis and ovarian teratoma, followed by NMOSD one year after tumor resection. Her serum harbored anti-NMDAR and anti-AQP4 IgG antibodies. Anti-NMDAR antibody assessments in the CSF were positive. Ran et al. (2017) reported a 30-year-old male patient with anti-NMDAR encephalitis followed by seropositive NMOSD. Fan et al. (2018) characterized myelin oligodendrocyte glycoprotein-antibody (MOG-ab) disease and AQP4-IgG-positive NMOSD during anti-NMDAR encephalitis. Amongst the 491 NMOSD patients in the database, 435 patients were positive for serum AQP4-IgG, and 3 patients had coexisting CSF-positive NMDAR antibodies. The course of disease in 2 of the patients included anti-NMDAR encephalitis followed by NMOSD or recurrence. In a single patient, these occurred simultaneously (Table. 1).

4. Discussion

We describe a case of a female Chinese patient who presented with two distinct autoimmune diseases simultaneously: NMOSD with AQP4-IgG-seropositivity and anti-NMDAR encephalitis with positive NMDAR antibodies in the CSF. The patient had 3 of the 6 core clinical characteristics, including optic neuritis, longitudinally extensive transverse myelitis (LETM) lesions associated with acute myelitis, cervical LETM extending into the medulla, with AQP4-IgG-seropositivity. Thus, the patient was diagnosed with NMOSD. However, two aspects of her symptoms were inconsistent with NMOSD. Firstly, brain MRI showed abnormal signals in the cortex, particularly the left temporal lobe, which was inconsistent with the typical imaging manifestations of NMOSD. For example, large, confluent, unilateral, or bilateral subcortical or deep white matter lesions were observed (Wingerchuk et al., 2015). Secondly, NMDAR antibodies were present in the CSF. A diagnosis of definitive anti-NMDAR encephalitis could be made in the presence of one or more of the six major symptoms, following the reasonable exclusion of other disorders (Graus et al., 2016). As the disease progressed, the patient showed speech dysfunction, a decreased level of consciousness, and involuntary movements such as mouth opening and tongue extension, supporting the diagnosis of NMOSD coexisting with anti-NMDAR encephalitis. The observed hemianesthesia, dysarthrosis, and dysphagia 6 months prior to admission, in combination with demyelination in the medulla oblongata were considered a demyelination syndrome episode (DSE).

Cases with a co-occurrence of NMOSD and anti-NMDAR encephalitis showed the following characteristics. Firstly, patients were predominately females (10/11 female cases, 1/11 male cases). Secondly, NMOSD and anti-NMDAR encephalitis showed no chronological sequence according to clinical onset. Thirdly, only 1 patient had a history of ovarian teratoma. Fourthly, if the NMOSD patients had abnormal behavior, prominent psychiatric manifestations, lower levels of consciousness, cognitive dysfunction, seizures, oral-facial movement disorders, autonomic nerve dysfunction, or atypical supratentorial lesions, anti-NMDAR encephalitis should be considered and the presence of NMDAR antibodies should be investigated. Patients with anti-NMDAR encephalitis with non-typical symptoms or atypical paraventricular lesions should also be considered for possible demyelinating episodes (Titulaer et al., 2014). Finally, patients with double positive antibodies and anti-NMDAR encephalitis related symptoms responded well to first-line immunotherapy including glucocorticoids, gamma globulin, and plasma exchange. The modified Rankin scale (mRS) scores of the patients significantly improved, and second-line immunotherapy including immunosuppressive agents was required for the

Table 2
Clinical features in 5 patients with AQP4-IgG-seropositive NMOSD at onset followed by anti-NMDAR encephalitis, and 4 patients with anti-NMDAR encephalitis at onset followed by AQP4-IgG-seropositive NMOSD.

Source	Sex/ Age at onset, y	NMOSD-NMDAR Interval, mo.	Clinical characters of NMOSD				Clinical characters of anti-NMDAR encephalitis				Immunotherapy		mRS max	Last mRS
			Clinical features	MRI	AQP4-ab CSF/serum	NMDAR-ab CSF/serum	Clinical features	MRI	NMDAR-abCSF/ serum	AQP4-abCSF/ serum	NMOSD	NMDAR		
Titulaer et al.	F/8	84	Ep.1:bilateral ON, Ep.2:LETM	n.d.	+(1:160)/+(1:10,240)	n.a.	Fluctuating levels of consciousness, seizures, paranoia, dystonia, orofacial dyskinesias, coma, autonomic symptoms, spasticity	Multifocal increase in T2 signal in putamen, internal capsula, subcortical insula, hippocampi, and temporal regions, bilateral optical and cervical atrophy	+/+	n.a.	Untreated	Oral st, IVIG, PLEX, CTX, RTX	5	6[a]
	F/13	11	Recurrent LETM	T2 FLAIR increase from medulla to C5	+(1:160)/n.d.	n.a.	Seizures, altered behavior, memory, speech dysfunction.	Transient mild FLAIR increased signal.	+/n.d.	n.a.	Oral st, CTX	Oral st	5	2
	F/37	30	Recurrent ON	n.d.	+(1:320)/+(1:10,240)	n.a.	Depression; behavior, memory, and sleep dysfunction, autonomic symptoms	Areas of increased T2/FLAIR signal in right caudate, right temporal lobe and frontal lobes	+/–	n.a.	Oral st, IFN	Oral st, PLEX, IVIG, RTX	5	2
	F/55	36	n.a.	White matter lesions in the brain and spinal cord	–/+(1:20)	n.a.	Seizures, blurred vision, encephalopathy; behavioral, memory, speech, sleep disorders, low consciousness	Unchanged	+/n.d.	n.a.	Oral st, IVIG	Oral st, IVIG	5	5
Luo et.al	F/19	10	Ep.1: dizziness, nausea, hypersomnia, temporarily pain in the right eye Ep.2: dizziness	T2/FLAIR hyperintense signals in bilateral medial temporal lobes, brain parenchyma surrounding the third ventricle (Ep.1) and left insular region, bilateral temporal lobes (Ep.2)	n.d./+	n.d./ –	Memory dysfunction, irritable, attention deficit, apathy, insomnia, intermittent grope action of right upper limb.	Hyperintense left basal ganglia on T2-weighted/T2-weighted FLAIR images.	+/+	+/+	IVMP, IVIG, oral st, AZA	IVMP, IVIG, AZA, RTX, st	3	0
Zoccarato et.al	F/50	–5	Ep.1: drowsiness, cervical itching, impaired gait, paraplegia, Ep.2: left-eye optic neuritis, Ep.3: weakness of the right limbs.	Multiple T2-weighted hyperintense lesions in the pons, hypothalamus, medulla oblongata, and cervical spine (Ep.1); new lesions in the pons and dorsal spine (Ep.3)	–/+(1:100)	+/+(1:32)	Subacute, short-term memory loss, confusion, behavioral changes	T2-weighted, hyperintense medial temporal cortex.	n.d.	n.d.	PLEX, IV st, oral st, AZA	Surgery[b], oral st	5	2

(*continued on next page*)

Table 2 (*continued*)

Source	Sex/ Age at onset, y	NMOSD-NMDAR Interval, mo.	Clinical characters of NMOSD				Clinical characters of anti-NMDAR encephalitis				Immunotherapy		mRS max	Last mRS
			Clinical features	MRI	AQP4-ab CSF/serum	NMDAR-ab CSF/serum	Clinical features	MRI	NMDAR-abCSF/ serum	AQP4-abCSF/ serum	NMOSD	NMDAR		
Ran et.al	M/30	–10	Acute and serious blurred vision in the left eye, with subsequent vision loss	T2-weighted and DWI hyperintense images with Gd enhancement in the left optic nerve	+/+	+/–	Anomic aphasia, memory loss, calculation disability	Multiple T2 hyperintense signals in the right parietal-occipital and left frontal lobes, temporal lobe, inferior horn of the later ventricle, and hippocampus without Gd enhancement	+/+	n.d.	IV st, PLEX	IVMP	2	0
Fan et.al	F/16	–20	Ep.1:acute myelitis Ep.2:ABS Ep.3:ABS	T2 hyperintense lesions in left basal ganglion, thalamus, hippocampus, and cerebral peduncle (Ep.1); left thalamus, and cerebral peduncle (Ep.2); around cerebral aqueduct (Ep.3)	Ep.1:+/+ Ep.3: +(1:1)/+(1:32)	Ep.1:+(1:32)/ –Ep.3:+(1:1)/ –	Fever, headache, dysphasia, psychosis, memory loss, cognitive decline	T2 hyperintense lesions in bilateral basal ganglia and bilateral thalamus; with T2 hypointense and partially enhanced lesions in the left basal ganglion.	n.a.	n.a.	IVMP, oral st, IVIG, MMF	IVMP, oral st	4	1
	F/25	–6	Ep.1:irritability, ABS Ep.2:short-term memory loss, psychosis, ABS Ep.3:lethargy, memory loss, personality change Ep.4:ON, ABS	T2 hyperintense lesions in brainstem, left hippocampus (Ep.1); left basal ganglion, hippocampus and medial temporal lobe, and right thalamus(Ep.2); brainstem(Ep.3); right cerebellum (Ep.4)	Ep.3: n.a./–Ep.4: –/+(1:10)	Ep.3:+(1:10)/ –Ep.4:+(1:1)/ –	Verbal reduction, irritability, abnormal behavior, psychosis, seizures.	T2 hyperintense lesions in the pons, right temporal lobe, hippocampus, periventricular white matter.	n.a.	n.a.	IV st, oral st, IVIG, IVMP,CTX, MMF	IV st, oral st	4	4

ab = antibodies (dilutions shown in brackets); ABS = acute brainstem syndrome; AQP4-IgG = Aquaporin 4 immunoglobulin G; AZA = azathioprine; CSF = cerebrospinal fluid; CTX = cyclophosphamide; F = female; Ep. = episode; FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium; IFN = interferon; IV = intravenous; IVIG = intravenous immunoglobulins; IVMP = intravenous methylprednisolone; LETM = longitudinally extensive transverse myelitis; M = male; max = maximum; MMF = mycophenolate mofetil; mo. = month; MRI = magnetic resonance imaging; mRS = modified Rankin scale; n.a.= not applicable; n.d.= not done; NMDAR = N-methyl-D-aspartate receptor; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; PLEX = plasma exchange; RTX = rituximab; st = steroids; y = year

[a] Died 4 months after onset of anti-NMDAR encephalitis.

[b] a hystero-adnexectomy with the removal of an ovarian teratoma.

onset of NMOSD. Together with the patient outcomes reported, we found that the prognosis of patients with co-morbidity was mainly caused by the sequelae resulting from demyelinating events such as NMOSD, and that the disability rate of demyelination was higher than that of anti-NMDAR encephalitis (Fan et al., 2018; Titulaer et al., 2014). Although both adopted similar immunotherapy methods, different immune mechanisms may lead to variable therapeutic responses and prognosis. Thus, compared to simple anti-NMDAR encephalitis, patients with co-morbidities require stronger immunotherapy and second-line immunosuppressive therapy must be initiated as soon as possible. The poor prognosis of this case may be related to the wide range of neurological lesions, the existence of severe autonomic nerve dysfunction, the poor response to first-line treatment. Besides, these symptoms of the change in consciousness during the treatment process and the occurrence of involuntary movements of the tongue and mouth may be related to the course of anti-NMDAR encephalitis.

NMOSD often co-exists with autoimmune disease, suggesting antibody mediated immune susceptibility and co-existing immune mechanisms. However, the specific mechanisms of NMOSD remain elusive. Only 1 patient showed a history of ovarian teratoma (Zoccarato et al., 2013), suggesting autoimmune abnormalities were the most likely cause of co-morbidity as opposed to tumor related factors. Gene susceptibility may also play a role in co-morbidity development. Studies have shown that anti-NMDAR encephalitis secondary to herpes simplex encephalitis is caused by exposure to antigens that produce an autoimmune response to the inflammation of neurons following infection. It is thus speculated that inflammatory demyelitis causes anti-NMDAR encephalitis through a similar mechanism (Armangue et al., 2013). In addition, in cases of anti-NMDAR encephalitis with positive AQP4 in which no corresponding symptoms are detected (Titulaer et al., 2014), the presence of autoantibodies does not necessarily suggest disease, and unknown pathogenic antibodies may be involved in the autoimmune mechanisms of the comorbidity.

The pathogenesis of NMOSD can result from astrocyte damage due to complement dependent cytotoxicity that is mediated by AQP4 antibodies or demyelinating lesions due to T cell mediated immunity (Jarius et al., 2014). The pathogenesis of anti-NMDAR encephalitis may be attributed to antibody cross-linking and capping and internalization of the NMDARs, leading to decreased receptor density and the reduced synaptic functions of neurons (Hughes et al., 2010). To-date, although basic studies have suggested a relationship between the two antibodies, their correlation in patients with co-morbidity remains limited. AQP4 deficiency can lead to an excessive release of glutamate into the synaptic space resulting in the excessive activation of NMDARs, significantly increasing the excitatory postsynaptic currents mediated by NMDARs in the amygdala (Yan-Kun et al., 2012). Immune complexes can be form between the AQP4 and NR3A subunits of the NMDAR, suggesting that AQP4 may be involved in NMDAR-mediated signaling (Min-xia et al., 2014). Increased levels of AQP4 can lead to the down-regulation of the NMDAR NR1 subunit (Christian et al., 2015). This suggests that AQP4 and NMDA may share functionality, the specific mechanisms of which now warrant further investigation. On the basis of immune susceptibility, autologous immunity may trigger complement dependent cytotoxicity mediated by AQP4 antibodies and the excessive activation of the NMDAR. This may contribute to the mechanisms of co-morbidity observed in this study.

In conclusion, this case provides further evidence for the occurrence of NMOSD with AQP4-IgG-seropositive overlapping anti-NMDAR encephalitis in a Chinese patient. Both AQP4 and NMDAR antibodies are useful biomarkers for disease diagnosis. Due to improvements in the detection technologies for autoimmune disease, the discovery rates of positive antibodies have and will continue to increase. The specific mechanisms of double positive antibodies remain elusive, and both the clinical features and imaging abnormalities of autoimmune neurological co-morbidities are superimposed, leading to difficulties during diagnosis. It is therefore necessary to improve our understanding of atypical symptoms and imaging manifestations, and to examine relevant antibodies as early as possible to guide both treatment and prognosis. The potential diagnosis of co-morbidities should also be considered to prevent the generalization of diagnosis in the clinic.

Ethics approval and consent to participate

The study was approved by our local ethics committee.

Consent for publication

Written informed consent was obtained from the patients' representatives for the publication of this case report.

Conflict of interest

The authors declare that there are no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Shuxin Tao: Data curation, Formal analysis, Project administration, Writing - original draft. **Yan Zhang:** Conceptualization, Methodology, Writing - review & editing. **Hong Ye:** Investigation, Validation. **Dong Guo:** Data curation.

Data for reference

Datasets supporting the conclusions of this article are included.

Acknowledgments

Not applicable.

References

Armangue, T., Titulaer, M.J., Málaga, I., Bataller, L., Gabilondo, I., Graus, F., et al., 2013. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J. Pediatr. 162, 850–856.

Christian, G., Christian, R., Christoph, R., Andreas, W., Benedikt, G., Guido, S., et al., 2015. The intrinsic pathogenic role of autoantibodies to aquaporin 4 mediating spinal cord disease in a rat passive-transfer model. Exp. Neurol. 265, 8–21.

Fan, S., Xu, Y., Ren, H., Guan, H., Feng, F., Gao, X., et al., 2018. Comparison of myelin oligodendrocyte glycoprotein (MOG)-antibody disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) when they co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis. Mult. Scler. Relat. Disord. 20, 144–152.

Graus, F., Titulaer, M.J., Balu, R., Benseler, S., Bien, C.G., Cellucci, T., et al., 2016. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 15, 391–404.

Hughes, E.G., Peng, X., Gleichman, A.J., Lai, M., Zhou, L., Tsou, R., et al., 2010. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J. Neurosci. 30, 5866–5875.

Jarius, S., Wildemann, B., Paul, F., 2014. Neuromyelitis optica: clinical features, immunopathogenesis and treatment. Clin. Exp. Immunol. 176, 149–164.

Luo, J.J., Lv, H., Sun, W., Zhao, J., Hao, H.J., Gao, F., et al., 2016. Anti-N-methyl-d-aspartate receptor encephalitis in a patient with neuromyelitis optica spectrum disorders. Mult. Scler. Relat. Disord. 8, 74–77.

Min-xia, Z., Chao, L., Chun-mei, X., Zhong-wei, Q., Da-nian, Z., 2014. Simvastatin pretreatment protects cerebrum from neuronal injury by decreasing the expressions of phosphor-CaMK II and AQP4 in ischemic stroke rats. J. Mol. Neurosci. 54, 591–601.

Qin, K., Wu, W., Huang, Y., Xu, D., Zhang, L., Zheng, B., et al., 2017. Anti-N-methyl-D-aspartate receptor(NMDAR) antibody encephalitis presents in atypical types and coexists with neuromyelitis optica spectrum disorder or neurosyphilis. BMC Neurol. 17, 1.

Ran, Y., Wang, L., Zhang, F., Ao, R., Dong, Z., Yu, S., 2017. Anti-NMDAR encephalitis followed by seropositive neuromyelitis optica spectrum disorder: a case report and literature review. Clin. Neurol. Neurosurg. 155, 75–82.

Titulaer, M.J., Höftberger, R., Iizuka, T., Leypoldt, F., McCracken, L., Cellucci, T., et al., 2014. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor

encephalitis. Ann. Neurol. 75, 411–428.
Watanabe, M., Kondo, T., Murakata, K., Kageyama, T., Shibata, Y., Takahashi, T., et al., 2014. Antibodies to neural and non-neural autoantigens in Japanese patients with CNS demyelinating disorders. J. Neuroimmunol. 274, 155–160.
Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85, 177–189.
Yan-Kun, L., Fang, W., Wei, W., Yi, L., Peng-Fei, W., Jun-Li, X., et al., 2012. Aquaporin-4 deficiency impairs synaptic plasticity and associative fear memory in the lateral amygdala: involvement of downregulation of glutamate transporter-1 expression. Neuropsychopharmacology 37, 1867–1878.
Zoccarato, M., Saddi, M.V., Serra, G., Pelizza, M.F., Rosellini, I., Peddone, L., et al., 2013. Aquaporin-4 antibody neuromyelitis optica following anti-NMDA receptor encephalitis. J. Neurol. 260, 3185–3187.