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Letter to the Editor

Anti-neurofascin-155 antibody-positive neuromyelitis optica spectrum disorders

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Dear Editor,

1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is currently recognised as an inflammatory central nervous system (CNS) disorder that most frequently involves the spinal cord and optic nerve. Many studies have provided sufficient evidence for the importance of the AQP4 antibody in the pathogenesis of NMOSD [1,2]. In addition, other autoantibodies such as the AQP-1 and myelin oligodendrocyte glycoprotein (MOG) antibodies have also been found in NMOSD patients and have significant effects in the immune process of the disease [3]. Neurofascin-155 (NF155) is a protein expressed in both CNS and peripheral nervous system (PNS) myelin sheath. Studies have shown that the NF155 antibody plays an important role in chronic inflammatory demyelinating polyradiculopathy (CIDP) and combined central and peripheral demyelination disease [4,5]. In contrast, there have so far been no previous reports of concurrent NF155 and AQP4 antibody involvement in NMOSD. We herein present the cases of two patients with seropositive NMOSD, who carried of the NF155 antibody, which are mainly IgG1 and IgG2 subclasses.

2. Case presentation

2.1. Case 1

A 63-year-old Chinese woman with AQP4 antibody-positive NMOSD was admitted to our hospital in May 2015 due to high frequency relapse during the past 4 years. The patient exhibited severe disability, only light sensation in both eyes, and numbness and hypoalgesia below the sixth thoracic vertebra (T6) due to optic neuritis (ON) of both eyes and recurrent spinal lesions. Magnetic resonance imaging (MRI) demonstrated a T2 high-intensity lesion at T3–T5 (October 2014) and T3–T6 (March 2015) (Fig. 1A and B). There was no obvious abnormality in brain MRI. Electromyography (EMG) revealed slow sensory conduction velocities and longer F-wave latency at the tibial nerve (Table 1). The test for ganglioside antibodies showed positive results for GQ1b immunoglobulin G (IgG) by immunoblotting method using a commercial kit (Euroimmun, Germany). Other serological examinations showed no obvious abnormality. The patient did not undergo lumbar puncture examination at the acute stage. The cell-based assay (CBA) for the NF155 antibody showed positive results (Fig. 1E) [6], and the antibody subclasses were mainly IgG1 and IgG2 detected by enzyme-linked immunosorbent assay (ELISA). Treatment with rituximab was started in May 2015, and no relapse had occurred up to the time of writing.

2.2. Case 2

A 67-year-old Chinese woman without previous history of autoimmune disorders was admitted to our hospital in April 2011 because of rapid progression of muscle weakness and numbness in both legs. Neurological examination showed that her cranial nerves were spared. Muscle strength testing revealed a value of 4/5 (Medical Research Council grade) in both legs. There was impairment of sensation below the sixth cervical vertebra (C6). Articular clonus and positive Babinski signs were observed. The MRI of the brain was normal. But spinal MRI showed long spinal cord lesions from C5 to T5, and an axial image showed a T2 high-intensity lesion located mainly in the central grey matter (Fig. 1C and D). Cerebrospinal fluid examination revealed normal protein concentration and cell count. The CBA for serum AQP4 antibody showed positive results. Further, serum immunological testing showed positive results for the anti-nuclear antibody and anti-Sjögren's syndrome A and anti-Ro-52 antibodies. The rheumatoid factor increased markedly (595 IU/ml). Although Schirmer's test indicated low tear production (2 mm in 5 min, in both eyes), no relevant glandular biopsy data were available. The diagnosis of Sjögren's syndrome was not confirmed [7]. The patient was treated with high-dose methylprednisolone and intravenous immunoglobulin, and moderate improvement was observed in her legs. Since the first attack, she experienced six recurrences (one of ON and five of longitudinally extensive transverse myelitis), even with oral steroid and rituximab therapy, during the remission stage from 2012 to 2016. Since then, she had been treated with mycophenolate mofetil combined with low-dose steroids and she had not relapsed up to the time of writing. Serum NF155 antibodies were also detected using CBA (Fig. 1E). Further test results showed that IgG1 and IgG2 were the dominant antibody subclasses. The patient underwent EMG examination in October 2016, which showed that the motor and sensory conduction velocities were slightly decreased and the F-wave latency was mildly extended at the tibial nerve (Table 1). At the last follow-up, in February 2018, the muscle strength was 0/5 in both legs.

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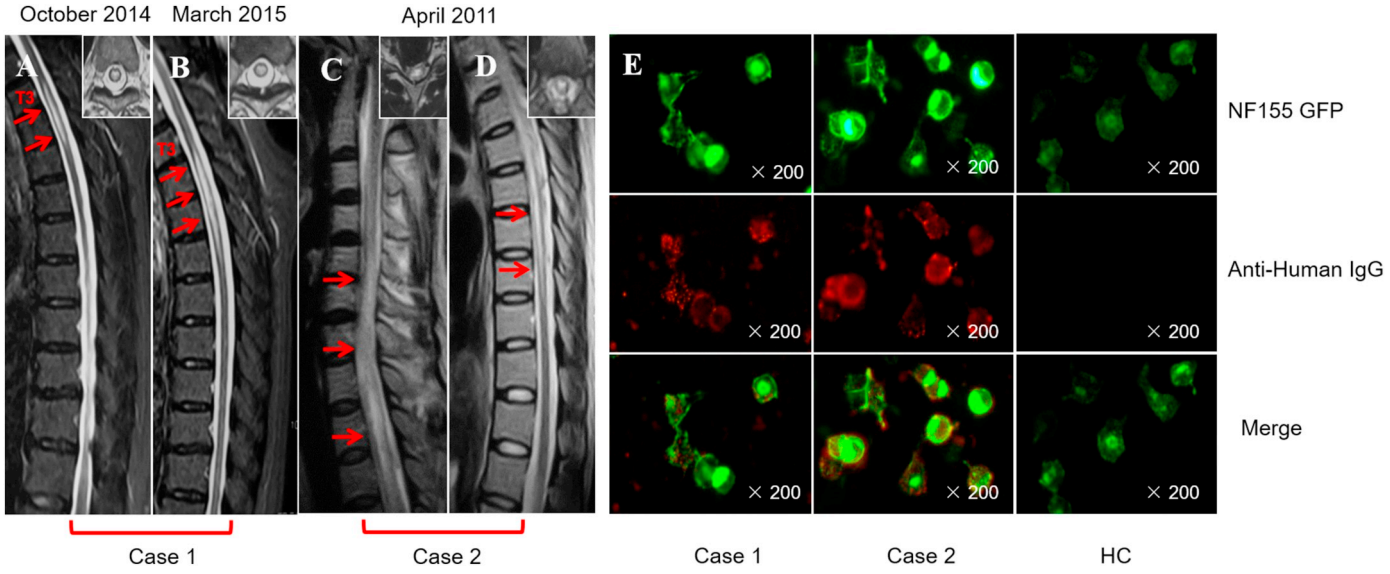

Fig. 1. Magnetic resonance imaging manifestations and cell-based assay for the anti-neurofascin 155 antibody in the patients. (A) Sagittal T2-weighted image of the spinal cord exhibits hyperintense lesions in the thoracic vertebrae, from the third thoracic vertebra (T3) to T5 levels. (B) Sagittal T2-weighted image of the spinal cord exhibits hyperintense lesions in the thoracic vertebrae from the T3 to T6 levels. (C, D) Sagittal T2-weighted image of the spinal cord exhibits hyperintense lesions in the spinal cord from the fifth cervical vertebra to T5. (E) The anti-neurofascin 155 (NF155) antibody binds to NF155. NF155-expressing cells were incubated with serum detected, followed by goat antiserum specific for human IgG. The colocalisation of the surface-expressed NF155 (green) and the anti-Human IgG antibody (red) indicates that the antibodies are against NF155 (Original magnification ×200). HC = healthy control. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Nerve conduction studies of two patients (data during remission).

	Motor										Sensory			
	CMAP(mV)		MCV(m/s)		DML(ms)		F wave				SAP(uV)		SCV(m/s)	
							Latency(ms)		Detection rate(%)					
	C1	C2	C1	C2	C1	C2	C1	C2	C 1	C 2	C 1	C2	C 1	C2
Ulnar L	6.6	8.4	60	53.7	5.8	7.7	26.3	26.5	100	100	8	6.8	53	48.6
Ulnar R	9.5	9.2	53	54.4	6.0	7.8	26.1	26.0	97	100	7	9.1	50	46.1
Normal value	> 8		> 50		< 4		< 28		/		> 10		> 50	
Median L	17.9	9.7	56	55.1	6.8	7.7	25.3	26.4	100	95	12	14.8	58	49.4
Median R	7.8	10.1	54	58.0	7.3	7.4	25.5	26.0	50.0	90.0	11	10.5	54	51.0
Normal value	> 8		> 50		< 4		< 28		/		> 10		> 50	
Peroneal L	3.7	3.4	40	40.9	10.4	13.7	/	/	/	/	22	15.0	48	41.4
Peroneal R	7.3	3.3	43	42.5	10.2	11.9	/	/	/	/	20	18.8	57	46.4
Normal value	> 3		> 45		< 5		/		/		> 10		> 50	
Tibial L	3.6	7.6	36	41.2	13.5	14.1	51.5	52.6	75.0	100	2	12.8	42	42.9
Tibial R	6.8	9.1	41	42.1	13.0	14.6	54.4	50.6	90.0	100	3	15.0	45	45.6
Normal value	> 5		> 45		< 6		< 50		/		> 10		> 50	

CAMP = compound motor action potential; MCV = motor conduction velocity; DML = distal motor latency; SAP = sensory action potential; SCV = sensory conduction velocity; L = left; R = right; C1 = case 1; C2 = case 2.

3. Discussion

In the present case study, we describe the cases of two female patients with NMOSD who tested positive for AQP4 and NF155 antibodies. The case reports suggest that the role of NF155 antibody in patients of NMOSD needs to be considered.

As an autoimmune inflammatory disease of the CNS that mainly involves the optic nerve and spinal cord, NMOSD causes severe neurological dysfunction. The finding of the AQP4 antibody in patients with NMOSD drives clinicians and scientists to focus on astrocytic inflammation and complement-mediated oligodendrocyte injury, with less concern for the function of the nodes of Ranvier, and the paranodal and juxtaparanodal regions. Expressed on the paranodal regions of the myelin sheath in both oligodendrocytes in the CNS and Schwann cells in the PNS, NF155 is indispensable for the interaction between myelin and axons. Immunofluorescence-based analysis of brain tissue revealed that NF155 distribution aligned with MOG in the subcortical white matter and was disrupted in demyelinating lesions in multiple sclerosis [8]. Another autopsy report also showed that NF155 levels were reduced in active multiple sclerosis lesions and led to disintegration of the paranodal junction [9]. However, there have been no reports of the damage to NF155 in NMOSD. We speculate that the NF155 antibody may cause destruction of the paranodal junction, thus aggravating the neurological deficits, together with the AQP4 antibody, in patients with NMOSD.

Similar to previous reports, our two NF155-positive patients also exhibited injury of the PNS, as indicated by EMG. Case 1 showed slow sensory conduction velocities and longer F-wave latency at the tibial nerves. Case 2 only showed minor problems in the PNS, possibly because the patient was not examined during the acute phase. Although

the symptoms that frequently occur in IgG4-subclass anti-NF155 antibody-positive CIDP, such as drop foot, gait disturbance, tremor, and symptoms of distal acquired demyelinating neuropathies, were not observed in our patients [10], disability due to the lesions in the CNS might have concealed these symptoms, and the IgG1 and IgG2 subclasses of anti-NF155 antibodies may have a distinct pathophysiology from IgG4-subclass anti-NF155 antibody-positive CIDP. In conclusion, the presence of NF155 antibodies and their subclasses should be noted in patients with NMOSD, especially when the EMG results show PNS injury. More importantly, further studies are needed to elucidate the pathogenesis of NMOSD in relation to the presence of the antibodies against AQP4 and NF155.

Author contributions

KJ, XZ, L-JZ, L-ML, YQ, CZ, C-SY and LY managed the patient; KJ and MY performed antibody detection; KJ drafted the manuscript; LY edited and revised the manuscript.

Competing interests

None.

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Patient consent

Obtained.

Ethical approval

The present study was approved by the Ethics Committee of Tianjin Medical University General Hospital.

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Kun Jia[a,b], Xu Zhang[a], Lin-Jie Zhang[a], Li-Min Li[a], Yuan Qi[a], Ming Yi[a], Chao Zhang[a], Chun-Sheng Yang[a], Li Yang[a,*]
[a] *Department of Neurology, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin 300052, China*
[b] *Tianjin Huanhu Hospital, Tianjin 300350, China*
E-mail address: yangli2001@tmu.edu.cn (L. Yang).

[*] Corresponding author at: Department of Neurology, Tianjin Neurological Institute, Tianjin Medical University General Hospital, No.154 Anshan road, Heping district, Tianjin 300052, China.