Multiple Sclerosis and Related Disorders 8 (2016) 74–77

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Case report

Anti-N-methyl-D-aspartate receptor encephalitis in a patient with neuromyelitis optica spectrum disorders

Jing-Jing Luo [a], He Lv [a], Wei Sun [a], Juan Zhao [b], Hong-Jun Hao [a], Feng Gao [a,*], Yi-Ning Huang [a]

[a] Department of Neurology, Peking University First Hospital, No. 8, Xishiku Street, Xicheng District, Beijing 100034, China
[b] Department of Neurology, Beijing Tongren Hospital, Capital Medical University, No. 1, Dongjiaominxiang Street, Dongcheng District, Beijing 100730, China

ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form
10 April 2016
Accepted 1 May 2016

Keywords:
Neuromyelitis optica spectrum disorders
Anti-N-methyl-d-aspartate receptor encephalitis
Demyelination
Aquaporin-4
N-methyl-d-aspartate receptor

ABSTRACT

We described a female patient with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis occurring sequentially with neuromyelitis optica spectrum disorders (NMOSD). The 19-year-old patient initially presented a diencephalic syndrome with aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) and brain lesions which involving bilateral medial temporal lobes and periependymal surfaces of the third ventricle on magnetic resonance imaging (MRI). Ten months later, the patient developed cognitive impairment, psychiatric symptoms and dyskinesia with left basal ganglia lesions on brain MRI. Meanwhile, the anti-NMDAR antibodies were positive in the patient's serum and cerebrospinal fluid, while the screening tests for an ovarian teratoma and other tumors were all negative. Hence, the patient was diagnosed NMOSD and anti-NMDAR encephalitis followed by low-dose rituximab treatment with a good response. This case was another evidence for demyelinating syndromes overlapping anti-NMDAR encephalitis in Chinese patients.

1. Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder of the central nervous system associated with antibodies against aquaporin 4 (AQP4-immunoglobulin G [IgG]), and the International Panel for NMO Diagnosis (IPND) has just unified the terms of NMO and Neuromyelitis optica spectrum disorders (NMOSD) into NMOSD, and recommended revised diagnostic criteria for NMOSD (Wingerchuk et al., 2015). Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe autoimmune disorder associated with antibodies against the GluN1 subunit of the NMDAR (Dalmau et al., 2011). In this study, we describe the case of a Chinese female NMOSD patient who developed with anti-NMDAR encephalitis.

2. Case presentation

A previous healthy 19-year-old female experienced intermittent dizziness, memory deficit and behavioral changes. Eighteen months before admission, she had presented with dizziness, nausea, hypersomnia and temporarily pain in the right eye. Examination of cerebrospinal fluid (CSF) showed normal cell count, mild elevation of protein (66.1 mg/dL). Laboratory investigations demonstrated significant hyponatremia to a nadir of 114.6 mmol/L, and mildly elevated prolactin but otherwise normal cortisol, adrenocorticotropic hormone, luteinizing hormone, follicular stimulating hormone and thyroid studies. Electroencephalogram (EEG) showed increased slow wave activity. A T2-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI revealed hyperintensity in bilateral medial temporal lobes, the third ventricle and brain parenchyma surrounding the cerebral aqueduct (Fig. 1(A)). Treatment of hyponatremia, intravenous methylprednisolone pulse (IVMP) therapy (500 mg per day for 5 days), intravenous immunoglobulins (IVIG) therapy (0.4 g/kg per day for 5 days), and antiviral therapy were administered as viral encephalitis was highly suspected. Then she received gradually tapered oral steroids for three months, during the course of steroid therapy she was partially relieved and the MRI lesions disappeared. Both ten and six months before admission, she reported two episodes of dizziness and axial T2-weighted MRI indicated lesions in the left insular region and bilateral temporal lobes, but the lesions were not enhanced on T1-weighted MRI with gadolinium (Fig. 1(B)). The serum AQP4-IgG and anti-SS-A antibody were positive, while the serum anti-NMDAR antibodies (NMDAR-Ab) were negative. Hence, the diagnosis of NMOSD was made, treatment with oral azathioprine (50 mg per day for 1 month, then 100 mg per day for 2 months) was given and she was stable for the

* Corresponding author.
E-mail addresses: luojj1986@126.com (J.-J. Luo), cranehebmu@sina.com (H. Lv), sunweibjmu@163.com (W. Sun), zhj7509@163.com (J. Zhao), haohj1963@126.com (H.-J. Hao), gaofh2011@126.com (F. Gao), ynhuang@sina.com (Y.-N. Huang).

http://dx.doi.org/10.1016/j.msard.2016.05.002
2211-0348/

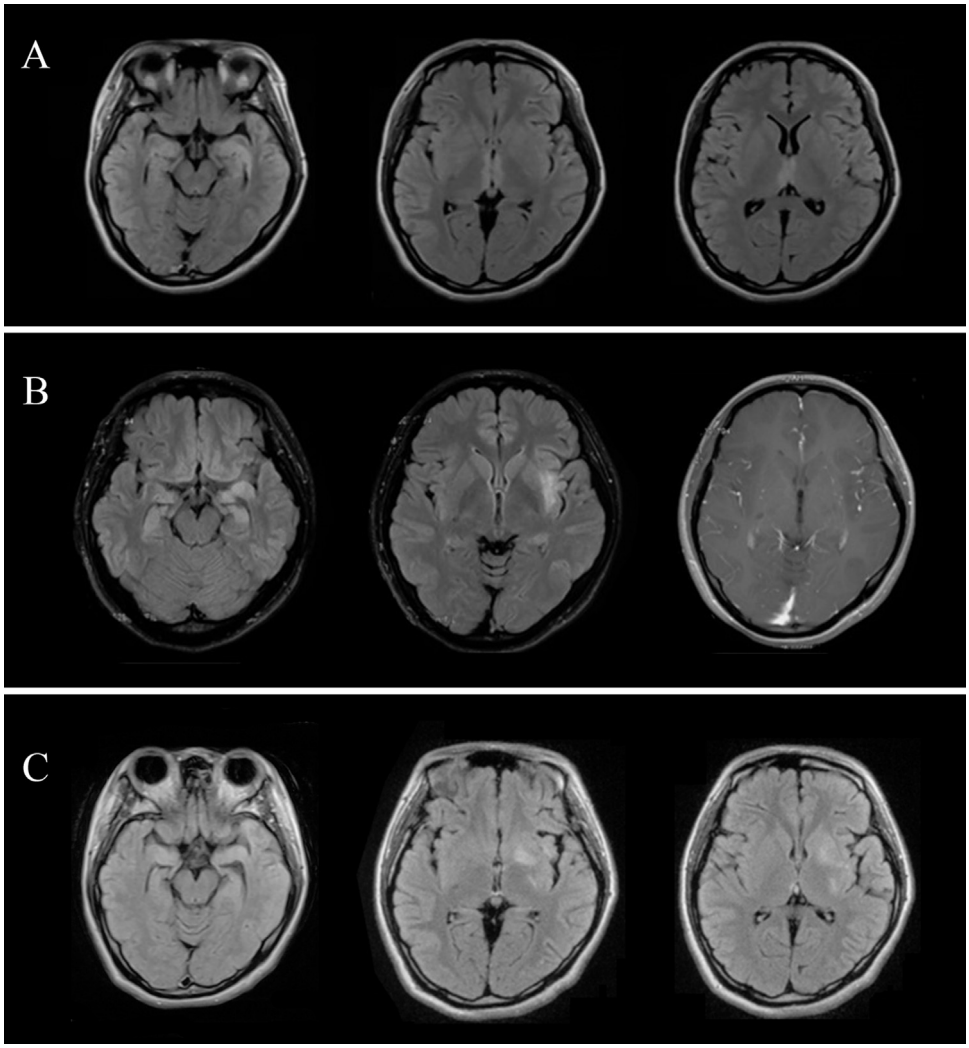

Fig. 1. Brain magnetic resonance imaging of the patient. (A) 18 months before admission, T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI shows abnormal hyperintense signals in bilateral medial temporal lobes and the brain parenchyma surrounding the third ventricle. (B) 10 months before admission, T2-weighted FLAIR MRI demonstrates lesions involving bilateral medial temporal lobes and left insular region without gadolinium enhancement. (C) During hospitalization, left basal ganglia lesions are depicted on T2-weighted FLAIR MRI, and the bilateral temporal lobes lesions are obviously relieved.

following three months.

Three months before admission, she complained of memory dysfunction, irritable, attention deficit, apathy, insomnia and intermittent grope action of right upper limb. She could not remember where she had put her bicycle, could not write an essay, and sometimes kept asking particular question. She also felt suffocated which could be released by inhaling oxygen. On admission, her consciousness was clear. Neurology examination noted abnormal time and place orientation, deficit in recent and short-term memory, other systems were normal.

Analysis of CSF showed lymphocytic pleocytosis (8 cells per milliliter), mild increased protein concentration (61.0 mg/dL) and IgG intrathecal synthesis rate (21.84 mg/24 h). The immunoglobulin G (IgG) index read 1.50, oligoclonal band was negative, and no evidence of any active viral infections. Her serum and CSF were tested for AQP4-IgG by indirect immunofluorescence and cell-based assay (CBA) on a commercial assay (Euroimmun, Lubeck, Germany) proving positive in both samples. Tests for classical onconeural antibodies (Hu, Ri, Ma2, CV2/CMRP5, amphiphysin, Yo) and antibodies to myelin oligodendrocyte glycoprotein (MOG) proved negative. The etiology of the patient's psychobehavioral symptoms was further examined, and the NMDAR-Ab was found positive in her serum and CSF, while the AMPAR-, $GABA_BR$-, LGI1- and CASPR2-antibodies were all negative. The anti-SS-A antibody was positive, and the antinuclear, anti-thyroid peroxidase antibodies were negative. EEG showed α wave frequency decreased. Brain MRI disclosed hyperintensity of the left basal ganglia on T2-weighted/T2-weighted FLAIR images (Fig. 1(C)). Ophthalmological examination showed delayed P100 latencies on both sides on visual evoked potentials. To investigate her feeling of suffocation, we performed a head-up tilt table test which identified she had postural orthostatic tachycardia syndrome (POST), suggested sympathetic hyperactivity. No cancer was found (gynecological ultrasonography, pelvic ultrasonography, positron emission tomography scan were all normal), especially ovarian original tumors were not detected. Although she had anti-SSA antibody, but she didn't complain generalized dryness, including xerostomia and keratoconjunctivitis sicca, and the salivary gland biopsy result did not support Sjögren's syndrome either.

We treated the patient with IVMP (1 g per day for 3 days, gradually tapered in 9 days), IVIG (0.4 g/kg per day for 5 days) and oral azathioprine (100 mg per day). The symptoms were partially relieved, her emotion stabilized and the involuntary movements decreased. After the IVMP therapy, we replaced oral azathioprine with intravenous rituximab (100 mg once a week for 4 weeks), then her percentage of $CD19^+$ B cells dropped to 0 in peripheral

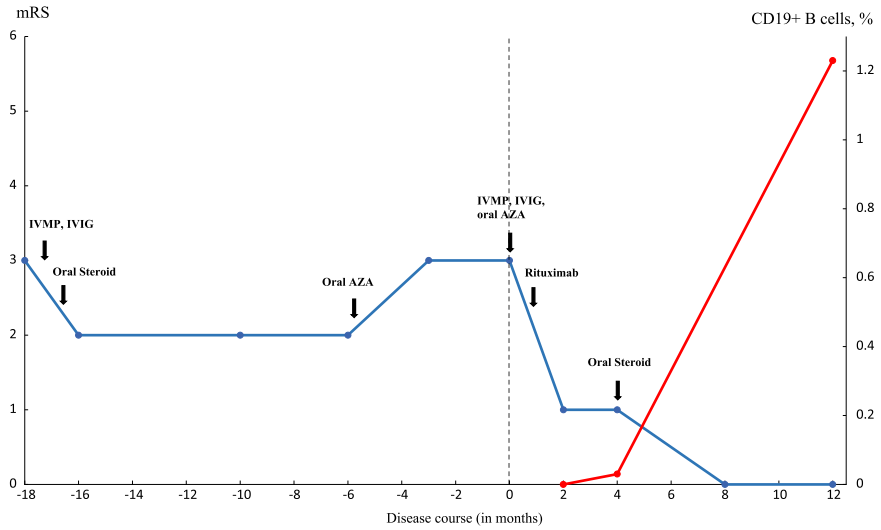

Fig. 2. Disease course and treatments of the patient. Time 0 on X axis marks the admission to our hospital and divides pre- and post-hospitalization periods. The clinical severities based on modified Rankin scale scores (mRS, solid line). The dotted line representing the percentage of $CD19^+$ B cells in peripheral blood after rituximab treatment. Arrow: intravenous methylprednisolone pulse (IVMP), intravenous immune-globulins (IVIG), azathioprine (AZA).

blood which measured with flow cytometry, the AQP4-IgG was still positive in serum, but the NMDAR-Ab turned negative in serum.

In the next two months, the patient's recent and short-term memory improved gradually, and the other symptoms disappeared. The AQP4-IgG turned negative in serum, the repopulation of $CD19^+$ B cells reached 0.03%, and there was no new lesions on the follow-up brain MRI. So she was given prednisolone (15 mg per day). Eight months later, AQP4-IgG was found in her serum again, meanwhile the percentage of $CD19^+$ B cells exceeded 1% (1.23%). However, the patient did not complain any new discomfort and exacerbation of symptoms. The physical examination, EEG, and the conventional MRI scanning brain and spinal cord were all negative. The clinical severities based on modified Rankin scale scores (mRS) was evaluated (Fig. 2).

3. Discussion

We describe this case of a Chinese female patient who developed anti-NMDAR encephalitis with good recovery during the course of NMOSD. The earlier clinical course of this patient met the international consensus diagnostic criteria for NMOSD and the later course was compatible with anti-NMDAR encephalitis. She presented diencephalon symptoms, and probable subclinical optic nerve involvement, positive test for AQP4-IgG using the CBA method. The brain MRI demonstrated lesions involving the hypothalamus, periependymal surfaces of the third and fourth ventricle and left internal capsule which are compatible with the NMOSD-typical brain lesion patterns (Kim et al., 2010; Pittock et al., 2006). So the patient was treated as NMOSD, and the clinical symptoms relieved by immunotherapy. Then the patient developed fulminant neuropsychiatric manifestations and behavioral dysfunction, and positivity for the NMDAR-Ab in serum and CSF, are atypical of NMOSD, which encouraged the diagnosis of anti-NMDAR encephalitis overlapping NMOSD.

A previous review reported that 3.3% anti-NMDAR encephalitis patients had prominent MRI and/or clinical features of demyelination, including 5 patients in whom anti-NMDAR encephalitis were preceded or followed by independent episodes of NMOSD (Titulaer et al., 2014). To the best of our knowledge, no similar case has been previously reported in China. Most noteworthy were the fact that all reported cases including this case, did not present with tumors, suggesting that patients were prone to autoimmunity. The patient was treated with low-dose rituximab, showed well tolerance and maintained good remission throughout the whole period of ten months, while the AQP4-IgG appeared again and the $CD19^+$ B cells exceeded 1%. It was reported a lower dosage of rituximab was efficacious in depleting B cells, maintaining low B-cell counts, and preventing disease progression in 5 Chinese NMO patients (Yang et al., 2013). Meanwhile, most studies recommend reinfusion of rituximab whenever the percentage of $CD19^+$ B cells reached 1% or the percentage of $CD19^+CD27^+$ B cells was higher than 0.05% instead of clinical relapse (Kim et al., 2013, 2011). However, one study revealed that AQP4-IgG titer and $CD19^+$ B-cell counts rise before relapse and fall with remission (Jarius et al., 2008), yet another study indicates that the suppression of disease activity by rituximab correlates with the extent of B-cell depletion, not with serum AQP4-IgG titer (Pellkofer et al., 2011). Above all, maybe the patient should receive additional rituximab infusion as soon as possible instead of waiting for another clinical attack.

Rituximab is also used as a second-line therapy for anti-NMDAR encephalitis (Titulaer et al., 2013). During the follow up of the patient, the symptoms of limbic encephalitis are improving, which suggests that a low-dose rituximab maybe also effective in anti-NMDAR encephalitis.

4. Conclusion

We report a Chinese patient developed non-tumor associated anti-NMDAR encephalitis with NMOSD, with a good response to reduced dosage of rituximab. It's a challenge for physicians to recognize anti-NMDAR encephalitis in NMOSD patients who mainly presented with brain involvement. Anyway, further investigations on the definite linkage between the two diseases are still in need.

Conflict of interest

The authors declare no potential conflicts of interest related to the research, authorship, and/or publication of this article.

Funding source

None.

References

Dalmau, J., Lancaster, E., Martinez-Hernandez, E., Rosenfeld, M.R., Balice-Gordon, R., 2011. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 10, 63–74.

Jarius, S., Aboul-Enein, F., Waters, P., Kuenz, B., Hauser, A., Berger, T., et al., 2008. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. Brain 131, 3072–3080.

Kim, S.-H., Huh, S.-Y., Lee, S.J., Joung, A., Kim, H.J., 2013. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol. 70, 1110–1117.

Kim, S.-H., Kim, W., Li, X.F., Jung, I.-J., Kim, H.J., 2011. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. Arch. Neurol. 68, 1412–1420.

Kim, W., Park, M.S., Lee, S.H., Kim, S.-H., Jung, I.J., Takahashi, T., et al., 2010. Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity. Mult. Scler. 16, 1229–1236.

Pellkofer, H., Krumbholz, M., Berthele, A., Hemmer, B., Gerdes, L., Havla, J., et al., 2011. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 76, 1310–1315.

Pittock, S.J., Lennon, V.A., Krecke, K., Wingerchuk, D.M., Lucchinetti, C.F., Weinshenker, B.G., 2006. Brain abnormalities in neuromyelitis optica. Arch. Neurol. 63, 390–396.

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.

Titulaer, M.J., McCracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., et al., 2013. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 12, 157–165.

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.

Yang, C.-S., Yang, L., Li, T., Zhang, D.-Q., Jin, W.-N., Li, M.-S., et al., 2013. Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. Neurology 81, 710–713.