

Case Report

Cortical demyelinating lesions in neuromyelitis optica spectrum disorders? A case study with 8-year follow-up

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Abstract: We present a rare case with initially presenting as the cortical lesions including hemianopsia, seizure, mental and behavioral abnormalities, and then gradually developed the symptoms and signs with typical optic neuritis and acute longitudinally extensive transverse myelitis. Although cortical lesions have been regarded as “red flags”, neuromyelitis optica spectrum disorders (NMOSD) was diagnosed preliminarily according to the clinical, laboratory and neuroimaging manifestations. The case has been followed up for 8 years so far (from 2008 to 2016). More importantly, this case study highlights the need for further research about the cortical demyelination in patients with NMOSD.

Keywords: Cortex, epileptic seizures, neuromyelitis optica spectrum disorders (NMOSD)

Introduction

Neuromyelitis optica (NMO) is a neuroimmunologic disorder mainly characterized by severe optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) [1]. In 2015, the International Panel for NMO Diagnosis (IPND) defined the unifying term NMO spectrum disorders (NMOSD) [2]. Several studies in magnetic resonance imaging (MRI) have revealed the consistent involvement of brain in the development of NMOSD [3]. However, cortical lesions have been regarded as “red flags” to diagnosis NMOSD and very few cases of NMOSD with cortical lesions have been reported. In this case study, we described a Chinese woman who showed the early symptoms of hemianopsia, seizure, mental and behavioral abnormalities. During the follow-up period, this patient gradually developed recurrent ON and LETM, and brain MRIs did not reveal typical multiple sclerosis (MS) lesions. In addition, antibodies against aquaporin-4 (AQP4) or myelin oligodendrocyte glycoprotein (MOG) were negative in either the serum or cerebrospinal fluid of this patient. The final observation ruled out alterna-

tive diagnoses but supported the diagnosis of NMOSD without AQP4-IgG.

Case report

A previous healthy 44-year-old Chinese woman abruptly developed right hemianopsia and could not see the outside top on March 10, 2008. Axial T2-weighted fluid attenuated inversion recovery (FLAIR) MRI showed high intensity signals in the left parietal lobe (**Figure 1A**). After one month, she was suffered from a generalized convulsion attack accompanied with unconsciousness and urinary incontinence. The epileptic seizures usually lasted for 40 to 60 seconds, and occurred at most by 20 times in a day. The patient received a single dose of diazepam (10 mg iv) followed by phenobarbital (0.2 g q.d im) and oral carbamazepine treatment (0.1 g q.d) for 10 days. After treatments, the seizures were stopped. In January 2009, she was suffered from a severe fever with shivering for a week. After treatment with anti-infections drugs, her situation was gradually improved. In April 2009, she showed the paroxysmal mental and behavioral abnormalities,

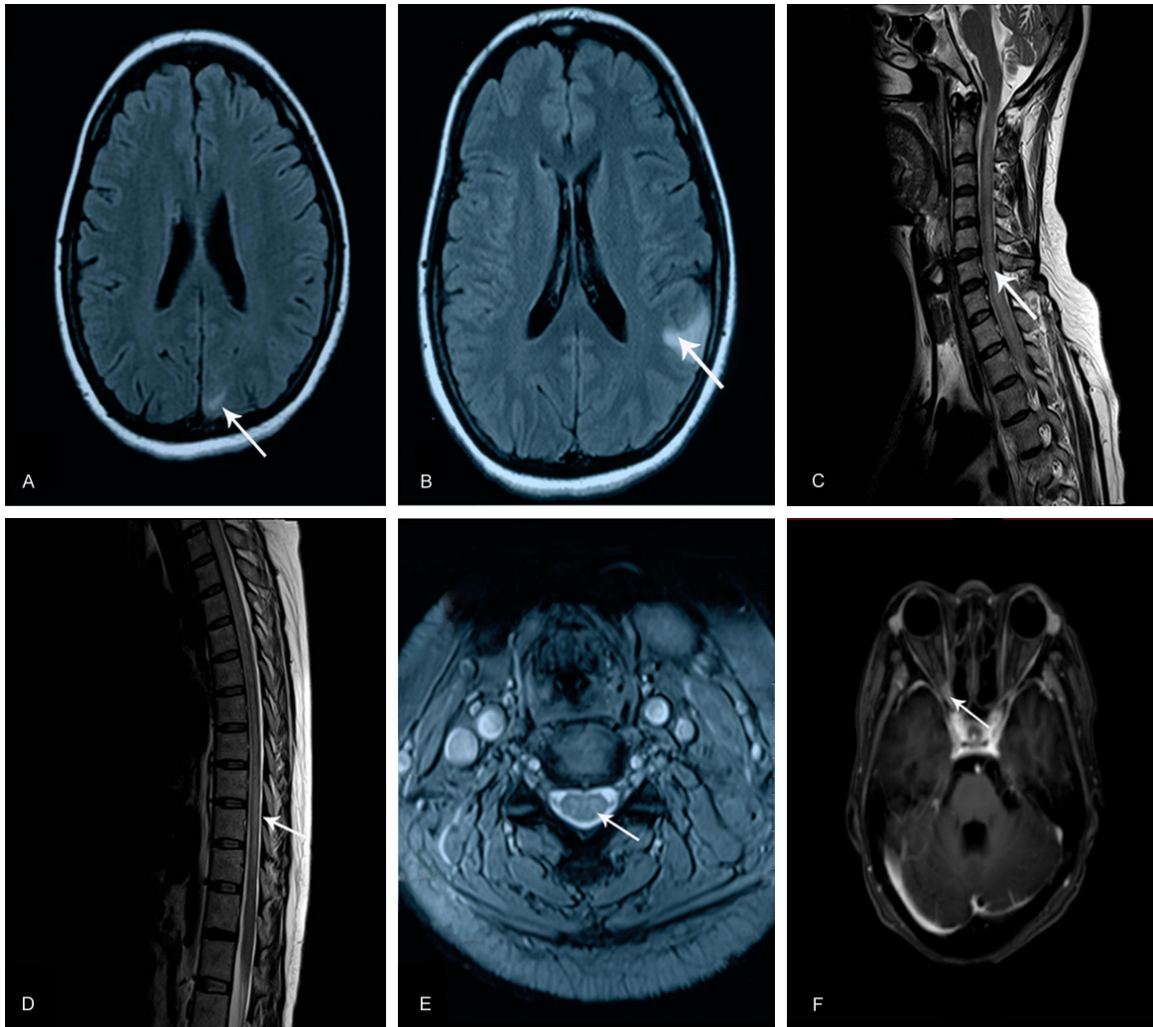


Figure 1. MRIs of brain and spinal cord during the follow-up period. (A: 2008) At the initial presentation, FLAIR imaging detected hyperintense lesions in the left parietal lobe (arrow). (B: 2009) After one year, repeated axial T2-weighted FLAIR MRI revealed abnormalities in the white matter of the left occipital lobe (arrow). (C, D: 2010) At the follow-up session after two years, Sagittal T2-weighted MRI of cervical and thoracic spinal cord showed hyperintensity signals in cervical 2-7 and thoracic 2-12 regions (arrows). (E: 2010) Axial T2-weighted MRI showed hyperintensity signals were located in the central gray matter (arrow). (F: 2015) Axial 3D T1-weighted contrasting images showed enhanced lesion in the posterior part of right optic nerve (arrow).

such as not knowing suddenly how going to toilet and how brushing her teeth, etc. The attack usually lasted for 1 to 2 min at the beginning and then it was gradually exacerbated and lasted for 10 min, and occurred by 20-30 times in a day. In addition, the seizures occurred at higher frequency (approximately 30 times per day) than previously. The seizure was cessation after treatment with antiepileptic drugs and her condition was gradually improved. However, her memory was declined at that time. Repeated axial T2-weighted FLAIR MRI revealed abnormalities in the left parietal lobe (**Figure 1B**). The

images revealed the lesions were primarily localized in the cortex and the manifestations of these lesions were changed over a period of time. This pattern of unstable cortical lesions in MRI suggested that the patient may develop mitochondrial encephalomyopathies (MELAS). To explore this possibility, we conducted muscle biopsy, metabolic examination, and genetic (blood mitochondria DNA A3243G, A8344G, T8993G/C, G13513A mutation) tests on the patient. The results did not support the diagnosis of MELAS. In August 2009, her condition was improved a little. In 2010, the patient

developed weakness in the lower limbs and she also accompanied with difficulty in urination and defecation. After treatment with intravenous methylprednisolone (1000 mg 5 d; 500 mg 3 d; 250 mg 3 d; 120 mg 3 d), the clinical symptoms were alleviated. Then, she received oral prednisone treatment with the dosage gradually decreased from 60 mg/day to 5 mg/day for several months. During the period, she could not walk and had been in bed. MRI scans revealed abnormal signals in the left frontal lobe and parietal lobe. Sagittal T2-weighted MRIs showed high intensity signals in the segment 2-7 of the cervical cord and the segment 2-12 of thoracic cord respectively (**Figure 1C, 1D**). Axial T2-weighted contrasting images showed high intensity signals in the central gray matter (**Figure 1E**). In September 2010, she had difficulty in urination and defecation once again. At the same time, intravenous methylprednisolone (1000 mg/d) was given for five-day. In March 2011, she lost vision in her right eye. After treatment with corticosteroid, her vision of the right eye was restored. At that time, a diagnosis of optic neuritis was made based on the clinical and image manifestations. In November 2011, she was admitted to the Intensive Care Unit in our hospital due to serious mental and behavioural disorders. But corticosteroid treatment did not show any effect. After 20 days, the clinical symptoms became a little better. After the myelitis attacked by 3 times in 2012, she was unable to do most activities of daily life and her condition was deteriorated rapidly. In January 2013, her symptoms were improved and became a bit better. At that time, the patient was able to walk a short distance without help or assistance. In March 2013, her symptoms further deteriorated, since she developed persistent urinary incontinence and walking difficulty. In September 2013, she started to treat with azathioprine (50 mg, p.o. twice a day with a gradual increase to 150 mg/day in two months) due to the frequent relapses of the disease. In the following months, she had been well and did not suffer from any relapse of the disease. However, two months after stopping azathioprine treatment by herself, she developed right-side optica neuritis in January 2015. Her vision gradually improved after treatment with a 14-day course of intravenous methylprednisolone (1000 mg 5 d; 500 mg 3 d; 250 mg 3 d; 120 mg 3 d) followed by oral prednisone treatment with

the dosage gradually decreased from 60 mg/day to 5 mg/day over several months. Axial 3D T1-weighted contrasting images showed enhanced lesion in the posterior part of right optic nerve (**Figure 1F**). She was treated with azathioprine (150 mg) orally twice daily for several months. So far she has not relapse of the disease.

Recently, the physical examination revealed a significant loss of motor function in both lower extremities (The muscle strength was graded as 1/5). Sensory deficits were found below the second thoracic level by performing a bobby-pin touch test. Routine laboratory investigations indicated that renal and liver functions were normal. The results of detecting autoimmune antibodies to anti-dsDNA, anti-nuclear, and anti-phospholipid antibodies were negative. The testing results of CSF revealed increased numbers of cells with 18 (normal range: 0-8 cells) and the levels of protein and glucose were normal. It was a pity that AQP4 antibody did not detect at early stage of the disease due to experimental conditions. However, antibodies to MOG and AQP4 were negative both in serum and CSF for two times at later stage of the disease.

Discussion

Initially, this patient had developed hemianopsia, seizure, mental and behavioral abnormalities. Later, she developed recurrent ON and LETM. MRIs revealed an enhanced lesion in right optic nerve and contiguous lesions extending over the three vertebral segments of spinal cord. Furthermore, brain images did not reveal typical MS lesions. These findings, coupled with the absence of antibodies against AQP4 or MOG, confirmed to make a final diagnosis of NMOSD without AQP4-IgG in this patient [2, 4]. Furthermore, in this case, the cortical demyelinating lesions may have contributed to seizures, which easily masquerading as MELAS due to the appearance of changed lesions in the cortex during initial stages.

Although there is abundant expression of AQP4 in normal cortex, pathology and imaging sensitive to cortical lesions have revealed their absence in NMOSD [5, 6]. It is noticeable that seizure is an important symptom in this patient. A Chinese study with a cohort of 69 NMOSD patients without developing any seizures sup-

ports the notion that seizure is an unusual feature in NMOSD patients in contrast to MS [7]. Moreover, the patient's overall presentation resembles three Japanese NMOSD patients [8]. Kim *et al.* introduced that the infiltration of inflammatory cells via the damaged blood brain barrier into the adjacent cortex may be one possible explanation of the cortical involvement [9]. Further evaluations are needed to push the boundaries of NMOSD by using advanced MRI techniques or pathological investigations to reveal the characteristics of cortex-involving lesions in NMOSD.

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Disclosure of conflict of interest

None.

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