A 50 Year-Old Woman with A Delayed Diagnosis of Neuromyelitis Optica Spectrum Disorder: The Clinical Course and Serial Neuroimaging Findings

Yu-Ju Huang, Wen-Neng Chang

Abstract

Purpose: Neuromyelitis optica (NMO) spectrum disorder and multiple sclerosis (MS) have similar clinical presentations which may make a diagnostic difficulty, especially when the data of aquaporin-4 (AQP4) antibody is not available. We reported the diagnostic and therapeutic dilemma of a woman with a delayed diagnosis of NMO spectrum disorder for more than 20 years.

Case report: The patient was a 51 years old woman who suffered from several episodes of relapsing and remission of limbs weakness, visual impairment and gait disturbance since 29 years old. She was diagnosed as a case of MS and received treatment accordingly. Treatment with the use of Rebif was started since 2008-2012, and was then shifted to Fingolimod due to several minor attacks were still noted during this period. Serum AQP4-IgG was checked before the use of Fingolimod by using Enzyme-linked immunosorbent assay (ELISA) and the result showed sero-negative for this Ab. However, occasional minor attacks were still noted. In May 2018, severe relapsing developed and brain magnetic resonance imaging (MRI) showed marked progression of the brain lesion. Initially, progressive multifocal leukoencephalopathy was suspected, but both cerebrospinal fluid and serologic study for John Cunningham virus (JCV) were negative. AQP4-IgG was rechecked by using cell-based assay (CBA), and the result showed positive finding. Thereafter, her therapy was changed to NMO spectrum disorder regimen.

Conclusion: It is worthwhile to recheck the serum AQP4-IgG if the initial study showed negative result by using ELISA since CBA has higher sensitivity than previous study method.

Keywords: Neuromyelitis optica, aquaporin-4 antibody, multiple sclerosis.

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INTRODUCTION

Neuromyelitis optica (NMO) spectrum disorder is an autoimmune demyelinating disease of the central nervous system (CNS) for which the aquaporin-4 (AQP4) water channels are the major target antigens [(1)]. The role of autoimmunity in the etiopathogenesis of NMO spectrum disorder was elucidated in 2004 after the discovery of

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AQP4 IgG which is an antibody (Ab) against the astrocyte water channel and is highly specific for this disorder [2]. The main clinical features of NMO spectrum disorder are optic neuritis and acute myelitis, and the others are area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy/acute diencephalic syndrome and symptomatic cerebral syndrome [1,3]. Multiple sclerosis (MS) is another important demyelinating disorder of the CNS, and the clinical presentations of MS are somewhat similar to that of NMO spectrum disorder [4,5], and this similarity has caused a diagnostic dilemma, especially in the era without the availability of the measurement of serum AQP4 IgG for referential consideration. Therefore, the detection of AQP4 IgG has been validated as a diagnostic criterion for NMO spectrum disorder in 2015 [6]. In this study, we reported the diagnostic and therapeutic dilemma of a 51 year-old woman with a delayed diagnosis of NMO spectrum disorder for more than 20 years+

CASE REPORT

The patient is a 51-year-old woman who suffered from several episodes of relapsing-remission of limbs weakness, visual impairment and gait disturbance since the year of 1998 while she was 29 years old and she was diagnosed as a case of MS and received steroid treatment thereafter. Despite under regular medical treatment, she had frequent relapsing of the clinical signs and symptoms and received in-hospital management at least five times. The available brain magnetic resonance (MR) imaging feature captured in the other hospital in 2002 is shown in Figure 1a, and no spinal MR imaging features were available. She visited our outpatient department (OPD) in 2007 for the second opinion and she received interferon beta-1a (Rebif) injection therapy during the time period of 2008-2012. The brain and spinal MR imaging features captured this time period are shown in Figures 1b-1d, 2a and 2b and Figures 3a-c, respectively. During this therapeutic time period, several minor attacks and at least four relapsing episodes with sensory symptoms were still noted; therefore, the therapeutic regimen was shifted to oral Fingolimod (0.5 mg per day) in 2012. Serum AQP4-IgG was checked before the use of Fingolimod by using Enzyme-linked immunosorbent assay (ELISA) and the result showed sero-negative for this Ab.

During the time period of Fingolimod treatment (2012-early 2018), about five relapsing episodes with abnormal sensory symptoms such as numbness and tightness of the limbs were still complained by the patient but the muscle power of the four limbs did not change and she still could walk independently. The brain MR imaging features captured in the time periods are shown in Figures 1e-1g and Figures 2c and 2d. In May 2018, severe relapsing with more weakness of the four limbs developed and brain MR imaging feature as shown in Figure 1h showed marked progression of the brain lesion. Follow-up MR imaging studies were performed in August and November 2018, which revealed regression of brain lesions (Figures 1i and 1j) and the spinal MR imaging features are shown in Figure 3d-g. Both CSF study and serologic study for John Cunningham (JC) virus were negative. Because of the clinical deterioration and the availability of AQP4-IgG detection by using cell-based indirect immunofluorescence assay, AQP4-IgG was rechecked and the result showed positive finding. Therefore, her therapy was changed to NMO spectrum disorder regimen with Azathioprine.

The latest neurologic examination performed on Feb 13, 2019 revealed impairment of bilateral visual acuity with a more severe impairment of left eye, weakness of four limbs with more severe involvement of lower limbs (MRC3-4), a decreased proprioception and vibration sensation of lower limbs. Her present expanded disability status scale (EDSS) is 6.

DISCUSSION

The traditional concept of NMO as described by Devic in the 1919 is a monophasic syndrome characterized by both bilateral optic neuritis and transverse myelitis (TM) occurring at the same time, or in quick succession, and a sparing the brain is emphasized [7]. But the discovery of auto-Ab biomarkers of the inflammatory demyelinating disorders of the CNS such as AQP4 Ab and myelin oligodendrocyte glycoprotein IgG (MOG-IgG) and the recognition that, despite some overlap, their clinical phenotypes are distinct from MS and have revolutionized the field of inflammatory CNS diseases [8]. In NMO spectrum disorders, AQP4 Ab can be found in approximately 80% of the patients with this syndrome, and a proportion of the other 20% may be accounted

for by other serum Ab biomarkers such as MOG-IgG [8]. AQP4 Ab is presently considered as a specific biomarker of NMO spectrum disorder allows its distinction from MS. Previously we used ELISA to measure the serum AQP4 Ab; but since 2018, we applied cell-based indirect immunofluorescence assay for its detection which may provide sensitive and highly specific diagnostic information for NMO spectrum disorders [9]. Cell-based indirect immunofluorescence assay is now a widely used method to detect AQP4 Ab in human serum with higher sensitivity and specificity than other anti-AQP4 IgG detection methods [10]. With regards to the sensitivity of the two detection methods in NMO spectrum disorder, cell-based indirect immunofluorescence assay (72.4%) has been reported to be higher than ELISA (51.7%), with a specificity of 100.0% and 98.6%, respectively [11]. In this patient, her initial serum AQP4 Ab checked in 2012 by using Elisa was sero-negative, but it become sero-positive in the follow-up study in 2018 by cell-based indirect immunofluorescence assay. This change of important biomarker from sero-negative to sero-positive could be related to the different methods with different sensitivity and specificity used for detection [9] and/or the different disease activity in the two study time points despite this association remains unclear [12].

Brain and spinal MRI study are important clinical tool for the diagnosis and disease activity follow-up for autoimmune inflammatory disorders of CNS such as NMO spectrum disorder. Typical NMO spectrum disorder MRI findings have been reported to be confluent hyperintensities on T2 FLAIR images that are usually asymmetrically distributed in periependymal and periaqueductal areas. One of the most specific brain features is lesions in the dorsal brainstem involving the area postrema, which is observed in 7%–46% of patients [13]. In our case, axial T2 FLAIR images showed multiple small ovoid periventricular lesions before the therapeutic regimen was shifted to Fingolimod in 2012 (Figures 1a-1e, 2a-2b), and there were few hyperintensity lesions close to the cerebral aqueduct, which is often observed in NMO spectrum disorder. Tumefactive brain lesions (Figure 2d) may be present in NMO spectrum disorder, but they are more common in MS patients [13].

Typical spinal cord lesions in NMO spectrum disorder are characterized by horizontal involvement of the spinal cord located centrally or both centrally and peripherally on axial images and involve more than 50% of the cord area. Compared with myelitis in NMO spectrum disorder,

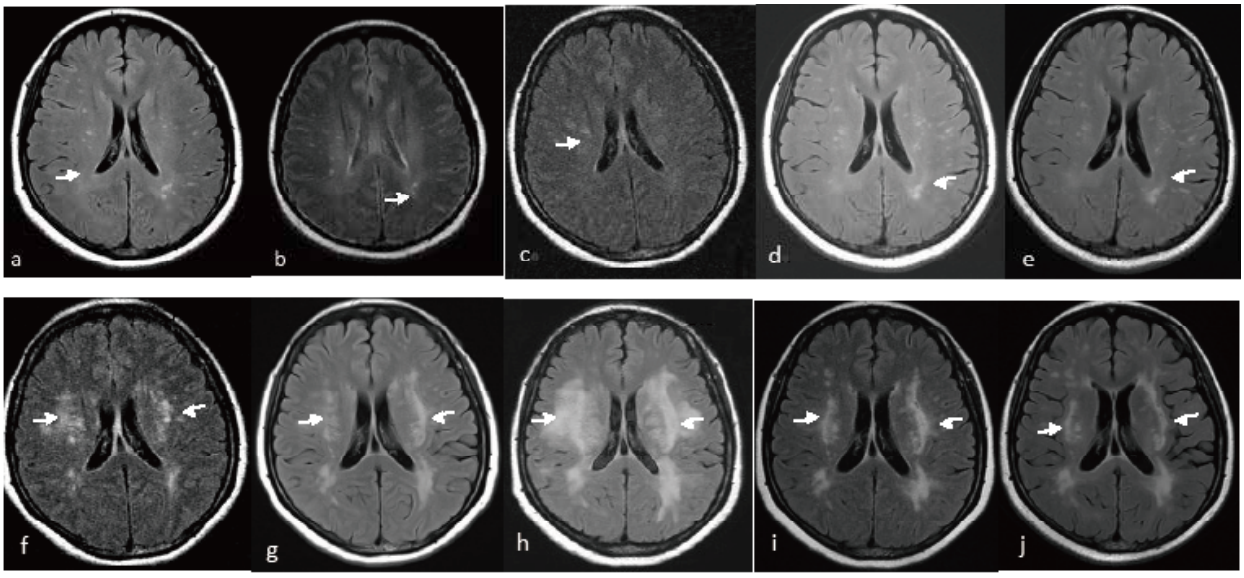

Figure 1. Cranial magnetic resonance imaging findings in 2002 to 2018.
All images are T2FLAIR. a, 2002; b, 2008; c, 2011; d, March 2012; e, August 2012; f, 2014; g, March 2018; h, May 2018; i, August 2018; j, November 2018. The arrows in the images (a to h) show the progression of bilateral hemisphere white matter lesions. The arrows in the image (i and j) reveal that the lesions showed partial remission after the patient received Azathioprine treatment (i-j).

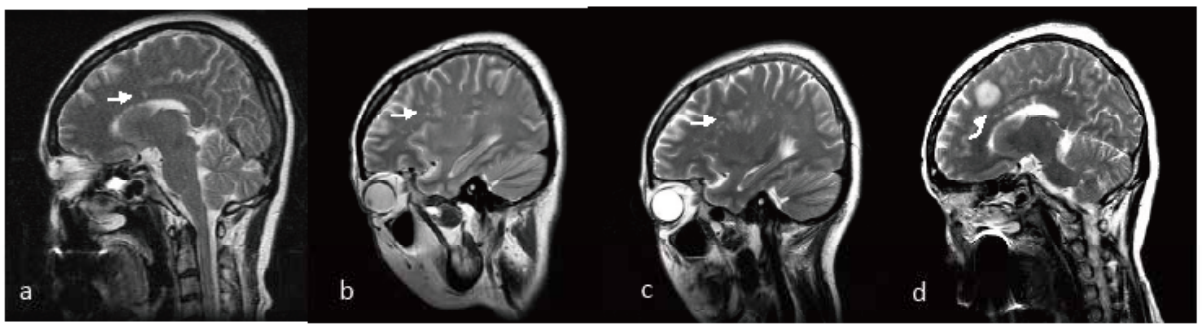

Figure 2. Sagittal view of cranial magnetic resonance imaging. All images are T2FLAIR. a, 2011; b, 2012; c, 2014; d, 2018. The arrows in the images show the progression of white matter lesions.

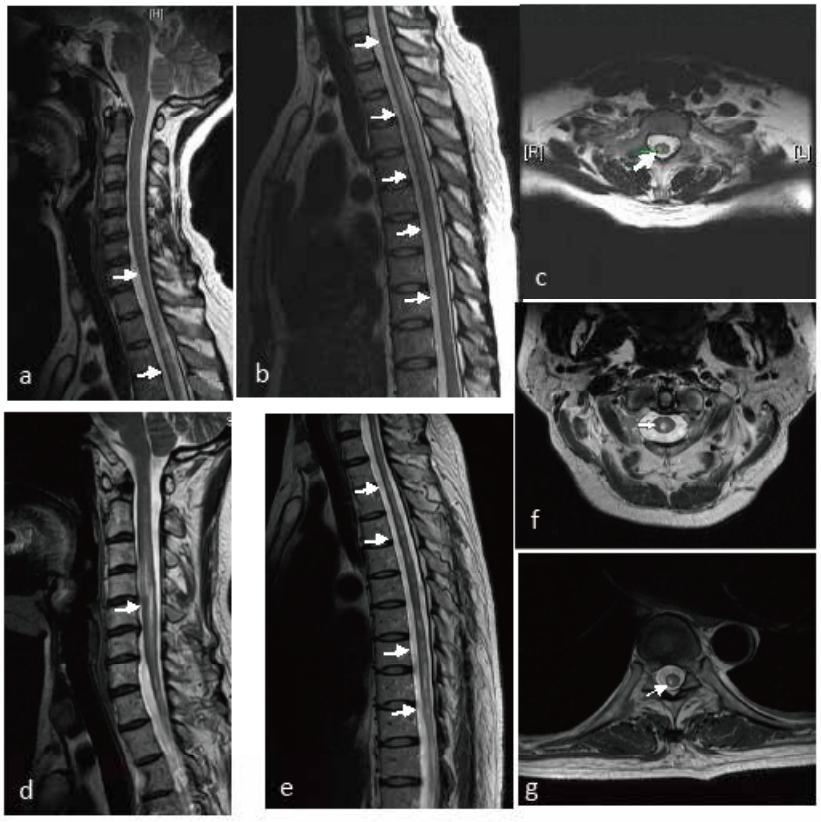

Figure 3. Spinal magnetic resonance imaging. All images are T2W1 sequence. a, 2008, C spine view; b, 2008, T spine view; c, 2008 C spine transverse view; d, November 2018, C spine view; e, November 2018, T spine view; f, November 2018, C spine transverse view; g, November 2018 T spine transverse view. The arrows indicate the lesions.

myelitis in MS usually has a more peripheral distribution which may be seen as dorsal or lateral lesions in the axial view of spinal cord MR imaging [13]. In the present case, the transverse views in 2008 (Figure 3c) and 2018 (Figures 3f-g) revealed that the lesions did not involve more than half of the cord area. The atypical finding in spinal MR imaging would have increased the difficulty of differentiating MS from NMO spectrum disorder if we had only depended on the MR imaging as the clinical tool for the diagnosis. Moreover, the NMO spectrum disorder

has a wide spectrum of neuroimaging spectrum and the numbers of neuroimaging features for this disorder has increased remarkably since the discovery of AQP4 Ab [14]; e.g. although the presence of longitudinally extensive transverse myelitis LETM is an important neuroimaging feature of NMO spectrum disorder, its incidence may vary greatly in different age groups of patients. The NMO spectrum disorder patients who had the clinical symptoms occurred two to three decades ago, as the situation of our present case had, may not receive suitable and adequate neuroimaging studies, the accurate diagnosis of NMO spectrum disorder might be misled.

In conclusion, in Taiwan, a positive detection serum AQP4 Ab by using cell-based indirect immunofluorescence assay should be considered in MS patient with a previous sero-negative AQP4 Ab detected by using ELISA, especially in those with a deteriorated clinical course despite with advanced therapeutic regimen.

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