Case Report

A Case of Neuromyelitis Optica Spectrum Disorder: Brainstem Involvement

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Summary

Neuromyelitis optica (NMO), or Devic's disease, which mainly affects the optic nerves and the spinal cord, is differentiated from the other demyelinating diseases by presence of NMO IgG/antiaquaporin-4 antibody (Anti-AQP4 Ab), poor prognosis, and absence of CSF oligoclonal IgG bands. Patients who do not meet the criteria for definite NMO, are considered as NMO spectrum disorders (NMOsd). Brain MRI lesions suggestive of NMO may be considered as an alternate supportive evidence for the diagnosis of NMOsd in patients with recurrent optic neuritis, longitudinally extensive transverse myelitis (LETM), recurrent brainstem, hypothalamic or encephalopathy symptoms, and AQP4-IgG seronegative status. We present a case with involvement of brainstem and cervical spinal cord and with NMO IgG positivity who considered as NMOsd together with the relevant literature.

Key words: Neuromyelitis optica spectrum disorders, anti-aquaporin 4 antibody, seronegative, brainstem, MRI

INTRODUCTION

Neuromyelitis optica (NMO), or Devic's disease, which mainly affects the optic nerves and the spinal cord, is differentiated from the other demyelinating diseases by presence of NMO IgG/antiaquaporin-4 antibody (Anti-AQP4 Ab) in up to 80% of cases, poor prognosis, and absence of CSF oligoclonal IgG bands. AQP4 is the most abundant water channel in the central nervous system, expressed in the foot processes of astrocytes in contact with blood vessels throughout the brain, spinal cord and optic nerves. Following identification of AQP4-IgG, it was
observed that 60% of the NMO patients presented signal abnormalities on brain magnetic resonance imaging\textsuperscript{(18)}. On the other hand, few patients show clinical characteristic features of NMO, without AQP4-Ab positivity\textsuperscript{(6)}. Patients who do not meet the criteria for definite NMO, are considered as NMO spectrum disorders (NMOsd)\textsuperscript{(23)}. Brain MRI lesions suggestive of NMO may be considered as an alternate supportive evidence for the diagnosis of NMOsd in patients with recurrent optic neuritis, longitudinally extensive transverse myelitis (LETM), recurrent brainstem, hypothalamic or encephalopathy symptoms, and AQP4-IgG seronegative status\textsuperscript{(11)}. Here, we wish to draw attention to NMOsd by means of a case with involvement of brainstem and cervical spinal cord and with NMO IgG positivity.

**CASE PRESENTATION**

Fifty five year-old male patient was admitted with hiccups, nausea, vomiting, dizziness, and imbalance. His medical history was unremarkable except for signs of an upper respiratory tract infection in the previous week. His neurological examination revealed gaze directed nystagmus, right sided limb ataxia and gait ataxia. The patient was initially diagnosed as ischemic stroke due to the lesion on the right lateral medulla oblongata shown by diffusion weighted magnetic resonance imaging (MRI-DWI). Cervical and intracranial MRI angiography and echocardiography findings were normal. Drowsiness, confusion, agitation, dysarthria, dysphagia, and weakness of the right arm developed within a few days and the second MRI showed that the T2 hyperintense lesion was extending from mesencephalon to the spinal cord (Fig. 1-2-3). The lesion was partly enhanced after contrast injection and another non contrast-enhancing lesion was seen in frontal deep white matter (Fig. 4-5). The cerebrospinal fluid (CSF) examination showed pleocytosis (70 lymphocytes/mm\(^3\)), normal protein level (27.7 mg/dl), and normal glucose level (94 mg/dl) with negative bacterial cultures. Differential diagnosis included brainstem encephalitis, neuro-Behçet, neurosarcoidosis, paraneoplastic disorders, connective tissue diseases and demyelinating diseases; therefore acyclovir (3x750mg/day), and methylprednisolone 1g/day were applied. The CSF IgG index was within normal limits; oligoclonal IgG bands, and viral serology (EBV, VZS, CMV, herpes simplex type 1-2) were negative. Also angiotensin-converting enzyme and adenosine deaminase levels of CSF were normal. Serum autoantibody screening, paraneoplastic antineuronal antibodies and autoimmune encephalitis antibodies were negative. Anti-AQP4 antibodies were tested using a combination cell-based and immunofluorescence assay (Euroimmun AG, Germany). In cerebrum and cerebellum sections there were fluorescent staining in vascular walls and pial surfaces. However AQP4 transfected cells showed no staining. Therefore, NMO-IgG was considered positive but Anti-AQP4 Ab was negative. Repeated examinations revealed similar results. For screening malignancies, PET examination showed normal findings. Neuro-Behçet was excluded since there were no systemic findings of Behçet's disease, ophthalmic examination was unremarkable and pathergy test was negative. On the third day of the treatment, the patient was more alert with decreased agitations and paresis. Corticosteroid and antiviral therapy were completed respectively to 10 and 14 days. At the 11th day of the treatment, the cranial and cervical MRI were clear (Figure 6-7-8). In the CSF examination, the number of cells was reduced (10 lymphocytes/mm\(^3\)). Bilateral P100 latencies were mildly prolonged (120.3 ms) in VEP examination. Moderate dysarthria and ataxia were persistent at the discharge of the patient.
**Figure 1-2-3:** MRI T2 sequences showing C1, C2, C3 cervical spinal cord hyperintense lesion extending to the right posterolateral medulla oblongata, posterior pons, mesencephalon, and left lateral of the 4th ventricle.

**Figure 4-5:** Increased signal intensity in the right frontal area of the deep periventricular white matter in MRI T2 images.

**Figure 6-7-8:** Second MRI performed 10 days after treatment normal signal intensity of brainstem and cerebellar hemispheres no pathological contrast enhancement.
DISCUSSION

NMOsd is a group of recently described severe demyelinating disorders accompanied and associated with NMO-IgG/ Anti-AQP4 Ab\(^{(12,23)}\). The patients who show NMO-like features but not fully meeting the diagnostic criteria of NMO\(^{(24)}\) are referred as NMO spectrum disease. Limited number of studies reported the prevalence of NMOsd as 1.5\%\(^{(5)}\).

The patients who have optic neuritis (ON) and transverse myelitis (TM) simultaneously can be easily diagnosed. In several cases ON and TM are presented as limited forms, mixed recurrent episodes or rarely as brainstem encephalitis\(^{(3)}\). Aquaporin-4 antibody seropositivity was found in 80\% of NMO patients in western series\(^{(8)}\), meanwhile high rate of seronegative patients are reported from middle east and meditteranean region\(^{(1,5)}\). A large number of patients with AQP4-IgG seropositive status who do not meet the 2007 definition of NMOsd were identified. This suggests that a wider range of clinical phenotypic presentations have to be included in an expanded spectrum of NMO, and a new classification will be helpful in diagnosing these patients\(^{(11,23)}\).

In this expanded classification, at least 1 of the following conditions; 1)Single, recurrent or simultaneous bilateral optic neuritis, 2) Longitudinally extensive myelitis, ( \(\geq 3\) vertebral segments), 3) Recurrent brainstem symptoms, 4) Recurrent hypothalamic symptoms, 5) Recurrent cerebral symptoms associated at least 1 of the following; 1)Positive AQP4-IgG serum status or 2)Brain MRI lesions typical of neuromyelitis optica have to be shown\(^{(11)}\).

Asymptomatic or symptomatic brain lesions were reported in 60\% of NMO patients. Most of these abnormalities were non-specific lesions, 10\% were multiple sclerosis-like lesions and 8\% were lesions atypical for multiple sclerosis\(^{(18)}\). High AQP4 expression in hypothalamus, ependymal surface of the third ventricle, aqueduct and fourth ventricle causes frequently bilateral lesions originating from these regions and also involvement of the posterior limb of the internal capsule and the cerebral peduncle. These lesions extend longitudinally, pursuing the pyramidal tract from subcortical area to the mesencephalon or pons\(^{(11,14,16,18)}\). Gadolinium-enhanced lesions show heterogeneous intensity and poor-defined borders. Brainstem lesions may be associated with intractable vomiting and hiccups\(^{(11,14)}\).

In a study, 77\% of 13 NMOsd patients had long extensive spinal cord lesions, 38\% had severe ON and 23\% had brain or brainstem lesions. Only 56\% had clinically definite NMO at follow-up. In a patient who applied with onset brainstem clinical findings, recurrent brainstem involvement was observed in the second attack. The authors concluded that a low prevalence of NMOsd among demyelinating disorders and a high occurrence of limited and atypical variants of NMO\(^{(5)}\).

In 2012, a large study from UK and Japan reported clinical outcomes and prognostic characteristics of 106 Anti-AQP4 Ab seropositive neuromyelitis optica patients. Kitley et al. showed that genetic factors influence the course of NMO. The UK cohort seemed to have more severe disease than the Japanese cohort, with more severe onset attacks, a higher relapse frequency and greater disability at follow-up, despite earlier immunosuppression\(^{(9)}\). In a multicentre study that investigators analyzed the clinical and paraclinical features associated with NMO spectrum disorders in Caucasians in a stratified fashion according to the patients' AQP4-Ab serostatus (AQP4-Ab positive in 78.3\%); 119 patients had a history of both ON and myelitis (seropositive in 77.3\%), 49 had a history of isolated LETM (seropositive in 81.6\%), 7 had a history of recurrent ON (seropositive in 71.4\%).
Bilateral ON at onset was more common in seronegative patients as well as simultaneous ON and TM. Moreover, a monophasic disease course is more often in seronegative patients. Seropositive patients were mostly female and more frequently had signs of coexisting autoimmunity, more severe clinical attacks, and an excessive load of spinal cord lesion than did seronegative patients. Motor symptoms, quadriplegia at the first myelitis attack and more than one myelitis attack in the first year were recognized as possible predictors of a poor prognosis\(^1,8\).

Our case had been diagnosed as ischemic stroke initially, but follow-up findings suggested brainstem encephalitis. The spinal cord lesions involving three segments and extending to the fourth ventricle, pons and mesencephalon were suggestive of NMO. Repeated examinations resulted as positive NMO-IgG antibody, but Anti-AQP4 Ab was negative. Clinical, laboratory, and MRI findings excluded systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis, Behçet's disease, tuberculosis, paraneoplastic and vasculitic diseases in the differential diagnosis but suggested NMOsd. In this case, typical brainstem lesions of NMO, NMO-IgG seropositivity, Anti-AQP4 Ab seronegativity and exclusion of other diseases lead us to NMOsd diagnosis. However, seronegativity in Middle East or Mediterranean area or atypical clinical features may complicate the diagnosis\(^1,19\).

Possible mechanisms of Anti-AQP4 Ab seronegativity is still unclear in these patients. Low antibody concentration, effect of immunosuppressant treatments, and more probably the presence of an antibody against a still unknown antigen may underlie the seronegativity\(^2,4,6,7,13,20,21\). According to some studies, antibodies against antigens other than AQP4, perhaps against other astrocyte targets may be present\(^17\). In a study conducted by Misu et al, suggesting

the secondary damage of myelin sheaths following astrocytic damage, in % 90 of NMO lesions glial fibrillary acidic protein (GFAP) loss was evident\(^15\). Therefore, more sensitive and wide range biomarkers are necessary for a better explanation of the immunopathogenetic mechanisms.

In conclusion, although aquaporin-4 antibody seropositivity is of great importance in the diagnosis of NMOsd, seronegativity alone cannot be sufficient to exclude the diagnosis. There is great need for future studies to clarify these issues.

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