

Detection of Autoantibodies against NMDA-Type Glutamate Receptor in a Patient with Recurrent Optic Neuritis and Transient Cerebral Lesions

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Key words

- autoantibodies against NMDA-type glutamate receptor
- recurrent optic neuritis
- demyelinating disease
- encephalopathy
- immunoglobulin therapy

Abstract

▼ We describe the case of a Japanese girl with recurrent optic neuritis and transient cerebral lesions. Antibodies against *N*-methyl-*D*-aspartate (NMDA)-type glutamate receptors were detected

in both serum and cerebrospinal fluid. Results of this case study suggest that the development of autoantibodies against NMDA-type glutamate receptors may play a role in the pathogenesis of central nervous system demyelinating diseases.

Introduction

▼ Optic neuritis occurs either singly or in concert with other widespread diseases such as central nervous system (CNS) demyelinating diseases. The mechanisms that cause demyelination are not fully known, but previous reports have suggested that autoimmune processes may play a crucial role [5,6]. The CNS demyelinating diseases involve various autoantibodies, suggesting that autoimmune responses are activated. Autoantibodies against *N*-methyl-*D*-aspartate (NMDA)-type glutamate receptor (GluR) have been detected in CNS inflammatory diseases [7–9]. To our knowledge, there is presently no evidence that CNS demyelinating diseases are associated with anti-GluR autoantibodies. Here we describe the case of a Japanese girl with recurrent optic neuritis and transient cerebral lesions in whom autoantibodies against NMDA-GluR were detected. We believe this is the first report to show that a demyelinating disease, recurrent optic neuritis, may be associated with anti-GluR autoantibodies.

lowing treatment with valproic acid, her seizures ceased. Upon examination of her past medical history, no abnormalities were found before the age of 10, and her mental and motor development were normal. At the age of 12, she suddenly lost vision in the right eye and developed eye pain. She was subsequently diagnosed with right optic neuritis and treated with steroid pulse therapy (methylprednisolone, 500 mg/day for 3 days). Thereafter, her optic neuritis improved markedly. About 2 weeks later, she began suffering from daily clusters of simple partial motor seizures in the left limb. The seizures occurred tens of times a day for several hours a day. During seizures she remained conscious and fully aware. These clusters lasted for one month. Following the serial addition of carbamazepine and clobazam to the valproic acid treatment regimen, her seizures ceased; however, these drugs could not be continued because of somnolence. Clobazam was thus discontinued, but she remained free of seizures. As soon as her seizures ceased, left optic neuritis occurred. Additionally, she presented with slurred speech and moderate ataxia. At that time, magnetic resonance images (MRI) were taken that showed gray matter with white matter lesions in the frontal lobe on fluid attenuated inversion recovery (FLAIR) images, and gadolinium-enhancing white matter lesions in the parietal lobe and in the left optic nerve on T₁-weighted images (○ Fig. 2). In subsequent MRI studies, these lesions were no longer observed. Spinal cord lesions were also not detected. Since that time, unilateral optic neuritis has recurrently

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Case Report

▼ A 12-year-old female was admitted to our hospital with recurrent optic neuritis (○ Fig. 1). At the age of 10, she had twice experienced generalized tonic-clonic seizures while awake. At that time, her interictal electroencephalogram (EEG) showed no sign of epileptiform discharges. Fol-

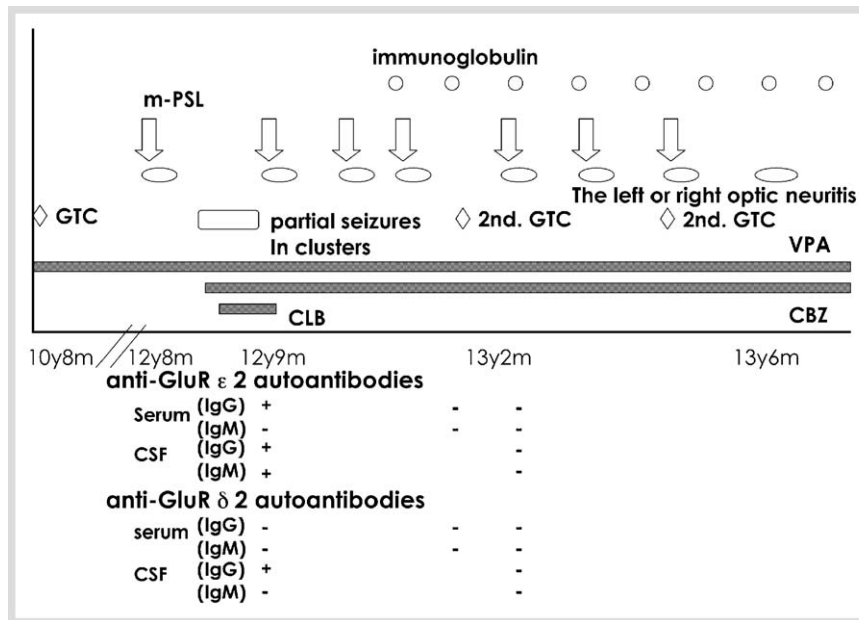


Fig. 1 The patient's clinical course, starting from the first episode of optic neuritis. In the first year, she had frequent optic neuritis. Although autoantibodies against NMDA-GluR were found in both serum and CSF during periods of clustered partial motor seizures, they disappeared about 2 months later. **m-PSL**: methylprednisolone pulse therapy. **2nd. GTC**: secondary generalized tonic-clonic seizure. **VPA**: valproic acid. **CBZ**: carbamazepine. **CLB**: clobazam.

occurred in the right or left optic nerve for a total of six times in the span of 1 year. During each episode, she presented with no apparent mental status change. In one instance, although she experienced partial motor seizures on the left side that progressed to secondary generalized tonic-clonic seizures followed by left optic neuritis (▶ **Fig. 1**), she immediately recovered consciousness after a short sleep. At that time, acute phase MRI revealed an enhanced left optic nerve lesion but no other brain lesion.

For each episode of optic neuritis, steroid pulse therapy was performed as previously described, and each episode was resolved over the course of several days to several weeks. Autoantibodies against GluR ϵ 2 and GluR δ 2 were detected in her serum and cerebrospinal fluid (CSF) at the time of the clustered partial motor seizures, using previously described methods [8] (▶ **Fig. 1**). For autoantibodies against GluR ϵ 2, immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies were both detected; however, only IgG type autoantibodies against GluR δ 2 were detected. These antibodies disappeared after approximately one month. Anti-microsome antibodies were also discovered, but anti-nuclear autoantibodies and anti-DNA (single- and double-stranded) autoantibodies were not detected. We also found no significant increases in any virus antibody titer. During the first episode of left optic neuritis, cell counts in the cerebrospinal fluid were increased (327/mm³), but oligoclonal band and myelin basic proteins were not detected. In addition, the CSF protein level, IgG level, and IgG index were not elevated (32 mg/dL, 2.7 mg/dL, and 0.6, respectively). However, no further abnormalities in cerebrospinal fluid cell counts have been detected since that time. Immunoglobulin therapy (0.25 g/kg/day) has been performed once per month to prevent frequent recurrent attacks. Since the administration of monthly immunoglobulin began, the frequency of her attacks has decreased, and novel abnormal lesions have not been detected on MRI scans for more than 2 years.

Discussion



According to the MRI data, our patient displayed both transient enhanced subcortical lesions in the right parietal lobe and recurrent lesions in the right and left optic nerves. Her symptoms included clustered transient left partial motor seizures and recurrent visual disorders. We considered the possibility of MS based on the dissemination of her lesions in time and space. Clustered partial motor seizures are seen in patients with Rasmussen syndrome but not in prototypic MS patients. MRI findings did not satisfy the McDonald MRI criteria [4], derived from Barkhof et al. [1] and Tintore et al. [10], for such a diagnosis. Transient cerebral lesions, clustered transient partial motor seizures, and pleocytosis suggested focal encephalitis. Thus, at present, her diagnosis is not considered to be conventional MS. Other possible diagnoses include a variant of acute disseminating encephalomyelitis (ADEM) and neuromyelitis optica (NMO). Krupp et al. described recurrent ADEM and multiphasic ADEM [3]. Although our patient presented with encephalitis only once, her other attacks included no encephalopathy or encephalitis. The MRI findings showed recurrent optic neuritis but no enlargement of the original lesions. Additionally, her attacks began with optic neuritis, and her MRI findings demonstrated no spinal lesion. Thus, her diagnosis is not ADEM or NMO.

In this case, immunoglobulin therapy was effective in decreasing frequent recurrences. Immunoglobulin therapy has been reported to be effective in decreasing attacks and improving the prognosis in MS, a demyelinating disease [2]; therefore, we thought this therapy might also be effective in the demyelinating process in this case. Although her diagnosis is not conventional MS, her condition may have a similar etiology.

Various autoantibodies have been detected in autoimmune demyelinating diseases, particularly MS [5,6]. However, to the best of our knowledge, there are no reports of autoantibodies against GluR in a demyelinating disease, including recurrent optic neuritis. This is the first report that a demyelinating disease, recurrent optic neuritis with transient cere-

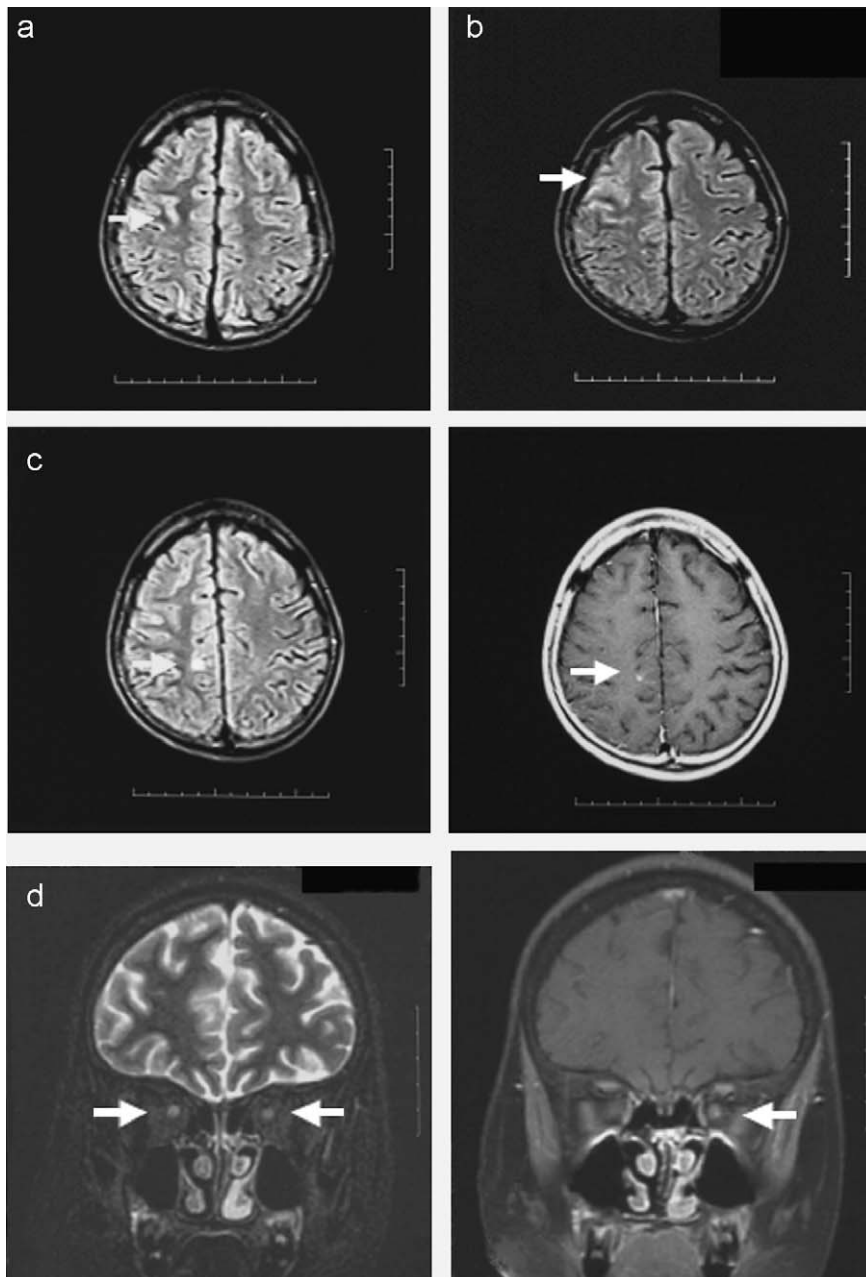


Fig. 2 MRI findings. Arrows indicate lesions. **a)** FLAIR image at 12 years, 9 months of age, showing right front-parietal subcortical lesion. **b)** FLAIR image at 12 years, 10 months, showing right frontal cortical and subcortical lesions. **c)** FLAIR image (left) and gadolinium-enhanced T₁-weighted image (right) at 12 years, 11 months. The right parietal subcortical lesion was enhanced by gadolinium. **d)** T₂-weighted image (left) and gadolinium-enhanced T₁-weighted image (right) at 13 years, with left optic neuritis. Bilateral optic nerve lesions are shown, and the left optic nerve lesion was enhanced by gadolinium.

bral lesions, may be associated with autoantibodies against NMDA-GluR.

Recently, autoantibodies against GluR have been found in various CNS diseases. For example, in acute viral encephalitis, GluR autoimmunity may contribute to the onset of localized encephalitis as well as the development of sequelae in widespread encephalitis [7]. Autoimmune processes, including the production of autoantibodies against neural molecules, may also contribute to subsequent processes following acute insults to the CNS that result in autoimmune neuronal damage [7].

In our patient, autoantibodies against GluR might be closely related with the clustered partial motor seizures, while the intervals between the first episode of optic neuritis and the clustered transient partial motor seizures associated with autoantibodies against GluR were extremely short. This suggested that autoantibodies against NMDA-GluR may be associated with the onset of recurrent optic neuritis. Activated autoimmune processes may also result in demyelination and

the production of autoantibodies against NMDA-GluR. Additionally, these changes may lead to the development of clustered partial motor seizures.

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