Letter to the Editor

Severe relapse of anti-NMDA receptor encephalitis 5 years after initial symptom onset

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Dear Editor

N-methyl-D-aspartate receptors (NMDARs) are proteins embedded in the membrane of post-synaptic neurons, and anti-NMDAR encephalitis is autoimmune encephalitis first proposed by Dalmau et al. in 2007 [1]. The disorder is characterized by abnormal behavior, cognitive dysfunction, seizures, disturbance of consciousness, central hypoventilation, and movement disorders, with a tendency to occur in younger women. Immunotherapy and tumor removal, where applicable, are effective for this disorder. However, previous papers have shown neurological relapse in 12–24% of cases [2–4]. We present a case of anti-NMDAR encephalitis relapse 5 years after the initial episode. Although the relapse was much more severe than the initial episode, she recovered with aggressive therapy using first- and second-line immunotherapies.

1. Case report

A 17-year-old girl with no history of illness presented with bizarre behavior and was admitted to a different hospital. She developed disturbance of consciousness and abnormal movements including oral dyskinesia and dystonia. Magnetic resonance imaging (MRI) of the brain and pelvis revealed no abnormalities. Electroencephalography showed diffuse slowing without epileptiform discharges. Cerebrospinal fluid (CSF) examination showed 38 white blood cells (all lymphocytes) with: glucose, 55mg/dL; protein, 42mg/dL; and IgG index, 1.22. Positive results were obtained for CSF anti-NMDAR IgG antibody (titers not recorded), leading to a diagnosis of recurrent anti-NMDAR encephalitis. She responded well to first-line immunotherapy. At the time of relapse, 5 years after the initial episode. In the first episode, the patient recovered with aggressive therapy using first- and second-line immunotherapies. Anti-NMDAR encephalitis could relapse with a more severe clinical course after several years. Aggressive immunotherapy including cyclophosphamide must be necessary even for recurrent cases of anti-NMDAR encephalitis.

2. Discussion

We have described a case of recurrent anti-NMDAR encephalitis 5 years after the initial episode. In the first episode, the patient responded well to first-line immunotherapy. At the time of relapse, however, the clinical course was more severe and resistant to the same first-line immunotherapy. She received 3 cycles of cyclophosphamide pulse therapy as second-line immunotherapy, finally leading to a good outcome.

Relapse was initially estimated to occur in 23–24% of patients with anti-NMDAR encephalitis, at a median of 2 years [2,3]. Relapse occurred more frequently in patients without tumor than in those with tumor, and predominantly in patients with either no immunotherapy or...
only steroid therapy. In a subsequent study of 577 patients with anti-NMDAR encephalitis, relapse rate within 2 years after onset had decreased to 12% [4]. This decline could be caused by better recognition of the disorder, earlier treatment, and increasing use of second-line immunotherapy. Patients who were also treated with second-line immunotherapy during the initial episode of anti-NMDAR encephalitis displayed fewer relapses. As an algorithm for the treatment of anti-NMDAR encephalitis, second-line immunotherapy is recommended for patients who did not respond to first-line treatment. Second-line immunotherapy is crucial not only to promote recovery, but also to decrease the frequency of relapses. In a comparison of severity between the initial episode and relapse, severity of symptoms was less severe in 67% of relapses, and symptoms at relapse were confined to one or only a few symptoms of anti-NMDAR encephalitis [4]. The severity of the initial episode was similar to that seen in the relapse in 23%, and was worse in another 10% [4]. Immunotherapy and clinical experience at the initial episode could decrease the severity of symptoms at relapse among the majority of recurrent patients. However, since over 30% of patients with recurrent encephalitis reportedly experience multiple relapses [4], monitoring should be continued with greater vigilance for patients showing clinical relapse once.

For the diagnosis of anti-NMDAR encephalitis, detection of anti-NMDAR antibody is essential. Antibody titers in patients with poor outcome are reportedly higher than in those with good outcome [5]. Although antibody titers decreased over time with the disease course in both groups, the decrease in titers was greater and occurred earlier in the CSF of patients with good outcome than in those with poor outcome [5]. In patients with relapse, clinical deterioration or recovery paralleled CSF antibody titers [5]. In this case, CSF samples were not obtained between the initial episode and the relapse. Further data are needed to evaluate the utility of anti-NMDAR antibody assay for predicting relapse and evaluating the need for immunotherapy in the chronic phase.

Anti-NMDAR encephalitis could relapse with a more severe clinical course after several years. Aggressive immunotherapy including cyclophosphamide must be necessary even for recurrent cases of anti-NMDAR encephalitis.

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**Authors’ contributions**

H.N. and U.K. examined the patient and wrote the manuscript. M.H. performed the analyses of antibodies. All authors read and approved the final manuscript.

**Disclosure**

None.

**Declaration of Competing Interest**

The authors have no conflicts of interest to declare.

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