We report the case of a young woman with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, without tumor, who was successfully treated with rituximab. Because conventional immunotherapy, including corticosteroids, immunoglobulin (IVIg), and plasma exchange showed little improvement in our patient, we introduced another treatment using rituximab. A week after the first administration of rituximab, her symptoms improved gradually and significantly. This case provides in vivo evidence that rituximab is an effective agent for treating anti-NMDAR encephalitis, even in those cases where conventional immunotherapies have been ineffective. Rituximab should be regarded as a beneficial therapeutic agent for this disease.

Key words: encephalitis, NMDA receptor, rituximab, treatment, tumor

Electropharmacology (EEG). Poor α organization with diffuse slowing of background activity was noted prior to the administration of immunotherapy, including rituximab (A). After rituximab was introduced, the abnormal activity on the EEG was markedly improved (B).
Dalmau’s laboratory (Department of Neurology, University of Pennsylvania), where the presence of anti-NMDAR antibodies was revealed on day 113. Therefore, she was diagnosed with anti-NMDAR encephalitis. Improvements of respiratory failure were relatively slow, and she was started on azathioprine (50 mg/day) treatment from day 160. On day 207, she was successfully weaned off artificial ventilation. Although disorientation and mild involuntary movement persisted, she was able to not only eat and walk unassisted, but also to draw a simple picture and write characters. On day 227, she was transferred to another hospital for rehabilitation.

![Figure 2](image_url)

**Figure 2.** Schematic representation of clinical course. The patient’s clinical symptoms improved consistently from a week after the first administration of rituximab.

![Figure 3](image_url)

**Figure 3.** Immunohistochemistry. Immunohistochemical observations on 10% formalin-fixed, paraffin-embedded sections of mouse cerebellar (A, B, C) tissue using a rabbit anti-glutamate receptor 52 (GluR2) antibody (sc-50415; Santa Cruz Biotechnology, Santa Cruz, CA, USA), at a dilution of 1:100 (A), the patient’s serum, at a dilution of 1:2,000 (B), and normal human serum, at a dilution of 1:2,000 (C). Prior to incubation with these primary antibody solutions, sections were microwaved (400 W, 95°C, 10 min) in citrate buffer, pH 6.0. Immunoreaction was visualized by the avidin-biotin-immunoperoxidase method (Vector) and polymer-immunocomplex method (Dako) for human- and rabbit-derived antibodies, respectively. 3,3′-Diaminobenzidine tetrahydrochloride was used as chromogen, and hematoxylin as counterstain. The patient’s serum samples were collected on day 57, prior to first administration of rituximab. The cytoplasm of Purkinje cells and the cerebellar molecular layer were distinctly immunopositive for the rabbit antibody (A), as well as for the patient’s serum (B). No immunoreaction was evident in the control section stained with normal human serum (C). GL: granular layer, ML: molecular layer, PL: Purkinje layer, Bars =10 μm
Although brain MRI did not reveal any abnormal intensities in this case, normal mouse brain parenchyma showed focal immunoreactions to serum samples from this patient that were collected on day 57 (after administration of first-line immunotherapy and before administration of rituximab) (Fig. 3). The cytoplasm of Purkinje cells and the dendritic layer were markedly immunopositive to the patient’s serum (Fig. 3).

Discussion

In this study, we describe the reduction in symptoms and EEG abnormalities in a young woman with anti-NMDAR encephalitis without an associated tumor by administration of rituximab. A previous report suggests that a tumor, mostly ovarian teratoma (2), could be identified in 42% of patients with anti-NMDAR encephalitis; however, no causative tumor lesions could be identified in the remainder of such patients. In patients without a tumor, first-line immunotherapy, using corticosteroids, IVIg, plasma exchange of such patients. In patients without a tumor, first-line immunotherapy and before administration of rituximab (22). Although infusion-related reactions, such as fever, were seen in this case, these resolved immediately, and there were no serious adverse effects during follow-up.

Cyclophosphamide is also recommended as second-line immunotherapy for anti-NMDAR encephalitis (2, 3, 8); however, dose-dependent gonadal toxicity and infertility might be serious disadvantages for young patients, in addition to the other negative side effects, including malignancy, hemorrhagic cystitis, myelosuppression, alopecia, and infection (23-26). Thus, considering the B cell-selective pharmacological effects and the limited side effects of rituximab, this therapy might be particularly useful in young anti-NMDAR encephalitis patients without tumor lesions (2, 5, 7, 13, 14, 20, 27-30).

More detailed clinical analysis is necessary to elucidate the etiology of anti-NMDAR encephalitis. Awareness of the probable effectiveness of rituximab for this type of encephalitis may both enhance our understanding of the disease and facilitate the appropriate treatment of patients with anti-NMDAR encephalitis.

The authors state that they have no Conflict of Interest (COI).

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References