CASE REPORT

Refractory Status Epilepticus Caused by Anti-NMDA Receptor Encephalitis that Markedly Improved Following Combination Therapy with Rituximab and Cyclophosphamide

Masato Kadoya, Hiroyuki Onoue, Akiko Kadoya, Katsunori Ikewaki and Kenichi Kaida

Abstract

We herein describe the case of a 48-year-old woman who presented with nonconvulsive status epilepticus refractory to antiepileptic drugs caused by anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis without any tumors. She developed nausea and psychiatric symptoms, followed by fever and an acute progressive disturbance of consciousness. On admission to our hospital, she presented with involuntary orofacial movements and central hypoventilation, and an electroencephalogram showed a generalized slow activity consistent with nonconvulsive status epilepticus. The patient’s drug-resistant status epilepticus markedly improved following second-line immunotherapy with rituximab and cyclophosphamide. Physicians should consider the early initiation of second-line therapy in certain cases of anti-NMDAR encephalitis.

Key words: status epilepticus, anti-NMDA receptor antibody, limbic encephalitis, second-line immunotherapy, rituximab, cyclophosphamide

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, a form of autoimmune limbic encephalitis associated with antibodies against heteromers of NR1 and NR2 subunits of cell-surface NMDA receptors, involves clinical features such as behavioral changes, memory deficits and involuntary movements (1-3). Titulaer et al. recently reported that approximately 80% of affected patients are women and that 40% have an underlying neoplasm (3). While seizures occur in 70% of patients and electroencephalogram (EEG) findings are abnormal in 90% of patients (3), status epilepticus has been reported in only 6% of cases (1), and there are several reports of refractory status epilepticus associated with anti-NMDAR encephalitis (4, 5). Although spontaneous improvements have been reported in some cases (6), almost all of these patients were treated with immunotherapy and/or tumor removal (1-3). It therefore remains to be elucidated as to which first-line therapy is most effective and when second-line therapy should be initiated following the failure of first-line treatment (3). We herein describe a case of anti-NMDAR encephalitis presenting with antiepileptic-resistant nonconvulsive status epilepticus that markedly improved following treatment with second-line immunotherapy.

Case Report

A 48-year-old woman infected with hepatitis C virus initially complained of nausea and was admitted to the department of gastroenterological medicine for treatment of hyponatremia. Two days after admission, she exhibited abnormal behavioral changes, such as altering the way she speaks, repetitively talking about the same things, frequently opening and shutting her mouth, blinking very rapidly and shouting loudly. Four days after admission, she was transferred to a mental hospital where she subsequently developed a high fever and rigidity. She was unable to follow commands and became unresponsive to external stimuli. One week later, she was admitted to our hospital. On admission, she pre-
pressed by the intravenous administration of anesthetic agents, such as propofol and midazolam. The patient was thus concurrently treated with first-line immunotherapy consisting of steroid pulse therapy (methylprednisolone: 1 g/day, three days) followed by oral prednisolone, the dose of which was subsequently tapered off, plasmapheresis (plasma exchange, two times) and intravenous immunoglobulin (400 mg/kg/day, five days, two courses), without any effect. We continued to administer the anesthetics and started treatment with second-line immunotherapy consisting of both weekly rituximab (375 mg/m², four times) and monthly cyclophosphamide (750 mg/m², three times) two months after admission. The NCSE markedly improved with the second-line therapy and was subsequently controlled with antiepileptic drugs alone following the tapering and cessation of the anesthetic agents. The patient awoke three weeks after the initiation of the second-line therapy and was subsequently weaned from ventilatory support three months after admission. The titer of anti-NMDA receptor antibodies in the CSF gradually decreased over time in correlation with the patient’s clinical course (Fig. 3). She was transferred to a rehabilitation hospital eight months after admission, without any neurological sequelae, except for mild disuse muscle atrophy. She has been free from relapse of epileptic seizures for one year, despite the tapering and cessation of the antiepileptic drugs. No ovarian tumors have been detected thus far.

Discussion

We herein described the case of a 48-year-old woman with anti-NMDAR encephalitis without any tumors who presented with NCSE refractory to antiepileptic drugs. Her clinical features, including the initial psychiatric symptoms, involuntary oro-lingual-facial movements and central hypoventilation (1-3), were compatible with a diagnosis of anti-NMDAR encephalitis; the exception being her age, as an age of onset of 45 years or over generally accounts for only 5% of all patients with this condition (3). Among cases of anti-NMDAR encephalitis, 46% of women have some kind of tumor, most often ovarian teratomas (94%). While brain MRI shows abnormal findings in only 33% of cases, EEG results are abnormal in 90% of patients (3). The abnormal EEG findings are characterized by generalized and/or frontotemporal predominant slow delta to theta waves (1, 2), consistent with the observations in this case. In addition, “extreme delta brush” was recently reported to be a unique EEG pattern in adults with anti-NMDAR encephalitis (7), although it was not detected in the present case. Various types of seizures occur in approximately 70% of patients with this type of encephalitis, whereas status epilepticus has been reported in only 6% of cases (1). To the best of our knowledge, only two cases of multidrug-resistant status epilepticus associated with anti-NMDAR encephalitis have been reported (4, 5). Kirkpatrick et al. stressed that an EEG pattern of rhythmic delta activity, as well as that of evolution, should be carefully assessed in order to obtain a correct di-
immunoglobulin are first-line agents, while rituximab and cyclophosphamide either alone or in combination are often employed as second-line regimens. In the largest cohort study reported to date (3), approximately half of all patients treated with a first-line immunotherapy and/or tumor removal showed symptom improvement within four weeks of treatment, with a good outcome at the two-year follow-up visit. Although there were no significant differences in the

Figure 2. Continuous EEG recordings obtained five days after admission under the intravenous administration of anesthetics agents showed a generalized rhythmic delta activity (A). The evolution of the EEG pattern was consistent with the patient’s ictal state and was more apparent when the EEG time base was double compressed (B).

Figure 3. Clinical course of the present patient. The NCSE disappeared after the initiation of second-line immunotherapy. As reported previously (12), the titer of anti-NMDA receptor antibodies in the CSF decreased in association with the improvements in the encephalitis. NCSE: nonconvulsive status epilepticus, PSL: prednisolone, PE: plasma exchange, IVIG: intravenous immunoglobulin, NMDAR: N-methyl-D-aspartate receptor, CSF: cerebrospinal fluid, NA: not available, *: - is negative at 1:200 dilution
Three Cases of Refractory NCSE with Anti-NMDAR Encephalitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
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<tr>
<td>4</td>
<td>35F</td>
<td>Ovarian</td>
<td>Teratoma</td>
<td>Cyclical pattern of moderate to high voltage, generalized, anteriorly biased 2 Hz alternating with 5-6 Hz sharp wave activity</td>
<td>PHT, VPA, LEV, BZD Propofol Pentobarbital</td>
<td>IVIG, RTX, CyC</td>
<td>Tumor removal</td>
<td>6 months</td>
</tr>
<tr>
<td>5</td>
<td>19F</td>
<td>Mediastinal</td>
<td>Teratoma</td>
<td>Continuous generalized rhythmic delta activity that evolved into ictal pattern over time</td>
<td>PHT, VPA, LEV, BZD, CBZ, PB, Felbamate Propofol Pentobarbital</td>
<td>Steroid, PE, RTX</td>
<td>Tumor removal</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Our case</td>
<td>48F</td>
<td>None</td>
<td></td>
<td>Generalized, frontotemporal predominant, rhythmic slow delta activity that evolved into ictal pattern</td>
<td>PB, LEV, TPM, LTG Midazolam Propofol</td>
<td>Steroid, IVIG, PE RTX, CyC</td>
<td>3 months</td>
<td>RTX, CyC</td>
</tr>
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efficacy of first-line immunotherapy between the patients with and without tumors in that study, this regimen appeared to be less effective in the latter group (2, 3).

According to another recent study (3), the addition of second-line immunotherapy is recommended in patients responsive to first-line immunotherapy in order to achieve superior outcomes. Although several case reports have indicated that both rituximab and cyclophosphamide are quite effective alone (8-10), we administered these drugs in combination in the present case based on the recommendation of Dalmau et al. (2), which resulted in a rapid clinical improvement in our patient. It is difficult to determine which regimen was more effective in this case, as previous reports have shown that both agents have an immediate effect on clinical symptoms (8, 9). This immediate effect may result from the more selective suppression of the antibody-secreting function of B cells than that achieved with first-line immunotherapy. It therefore remains to be elucidated whether rituximab and cyclophosphamide should be administered alone or in combination.

Kashyape et al. reported successful treatment with early aggressive cyclophosphamide therapy in two tumor-negative pediatric cases of anti-NMDAR encephalitis and postulated that the early introduction of second-line immunotherapy following the failure of first-line treatment reduces the duration of the illness (10). It is, however, a challenge to determine when to start second-line immunotherapy. In the present case, we should have initiated the second-line immunotherapy at an earlier stage, in that the NCSE markedly improved only after the introduction of the second-line therapy.

Three cases of refractory NCSE with anti-NMDAR encephalitis, including the present case, all involved women treated with multiple antiepileptic drugs and anesthetic agents (Table). In the two previously reported patients with teratomas, both the first- and second-line immunotherapy regimens were ineffective for NCSE, whereas tumor removal (4) and felbamate (NMDA receptor antagonist) administration (5) were ultimately effective. It is necessary to consider various therapeutic options for first- and second-line immunotherapy in addition to tumor resection, as responsiveness to treatment varies from case to case.

Among patients with anti-NMDAR encephalitis, the relapse rate ranges from 12 to 24% (1, 3, 11, 12). In one study, the anti-NMDAR encephalitis patients without tumors more frequently exhibited relapse than those with tumors over the two-year follow-up period, while the administration of second-line immunotherapy decreased the relapse rate (3). Therefore, yearly tumor surveillance should be applied for at least two years, even if no tumors are found on the initial presentation (2).

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

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References


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