

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

(Intern Med 54: 209-213, 2015)

(DOI: 10.2169/internalmedicine.54.2047)

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-

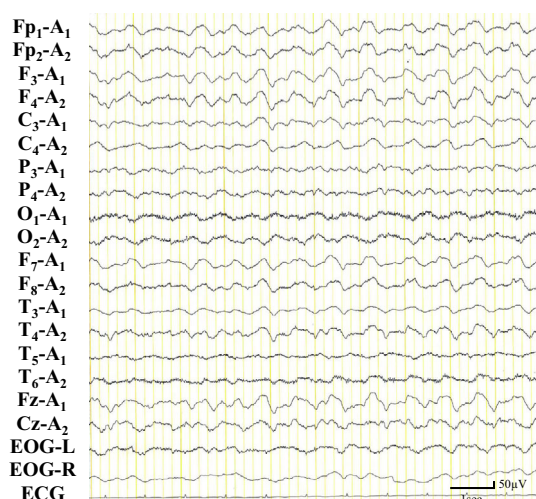


Figure 1. EEG performed on admission demonstrated a frontotemporal predominant generalized rhythmic delta activity.

sented with miosis, rapid blinking, involuntary oro-lingual-facial movements and rigidity in the neck and extremities. Her temperature was 38.0°C, and her respiratory rate was rapid and irregular, with features occasionally resembling hiccups. In addition, her level of consciousness was decreased (Glasgow coma scale score: 4), and an EEG showed almost continuous generalized rhythmic 2- to 3-Hz slow delta activity, predominantly in the frontotemporal region (Fig. 1). Posterior dominant alpha waves were absent, and the hematological findings were normal, with the exception of mild leukocytosis (11,200/ μ L) and hypercapnia (47 Torr). The cerebrospinal fluid (CSF) demonstrated mild pleocytosis (25/ mm^3), with a slightly elevated IgG index (0.81), although the glucose and protein concentrations were normal. No Herpes group viral DNA was detected in the CSF. Tests for anti-neuronal autoantibodies, such as anti-Hu, Yo, Ri, amphiphysin, Ma2, recoverin and voltage-gated potassium channel (VGKC) antibodies, were negative, except for NR1/NR2 heteromers of the NMDA receptor in the CSF and serum. Brain MRI showed non-specific areas of scattered hyperintensity primarily in the periventricular white matter on T2-weighted imaging and fluid-attenuated inversion recovery imaging without gadolinium enhancement. No tumors, including ovarian teratomas, were found, despite comprehensive tumor screening with repeated contrast enhanced CT and a complete gynecological examination, including pelvic ultrasonography and MRI. We therefore made a diagnosis of anti-NMDAR encephalitis without tumors.

The patient was intubated and monitored with continuous EEG, which showed generalized rhythmic delta activity (Fig. 2A), with an evolution pattern consistent with nonconvulsive status epilepticus (NCSE). This evolution pattern was more apparent when the EEG time base was compressed (Fig. 2B). The NCSE was found to be refractory to multiple antiepileptic drugs, including levetiracetam, phenobarbital, topiramate and lamotrigine, and incompletely sup-

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/ m^2 , four times) and monthly cyclophosphamide (750 mg/ m^2 , 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-

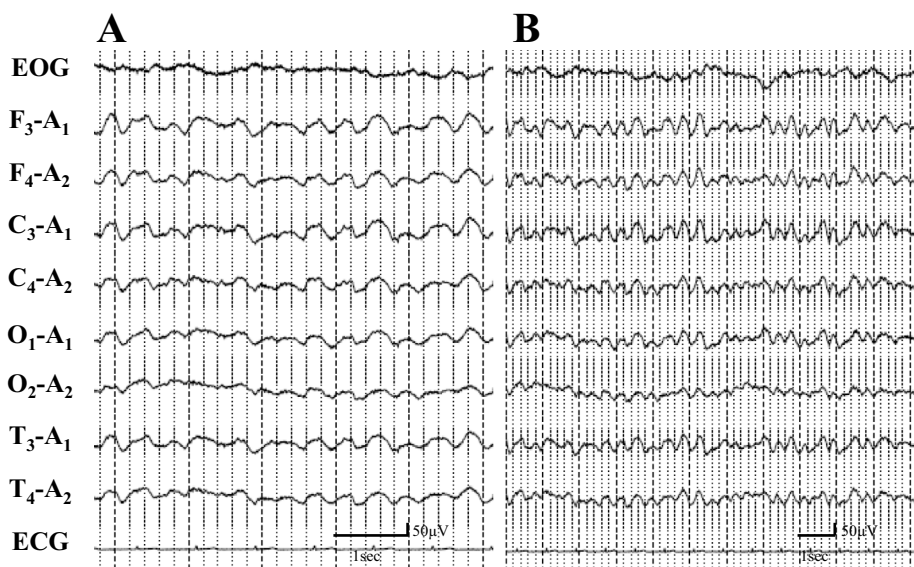


Figure 2. Continuous EEG recordings obtained five days after admission under the intravenous administration of anesthetic agents showed a generalized rhythmic delta activity (A). The evolution of the EEG pattern was consistent with the patient’s ictal state and was more apparent when the EEG time base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

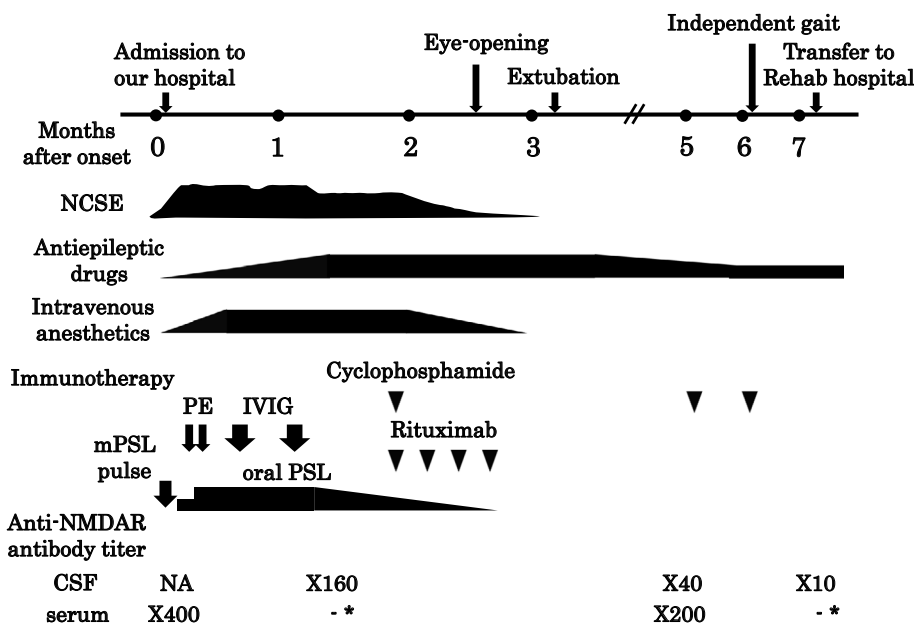


Figure 3. Clinical course of the present patient. The NCSE disappeared after the initiation of second-line immunotherapy. As reported previously (12), the titer of anti-NMDA receptor antibodies in the CSF decreased in association with the improvements in the encephalitis. NCSE: nonconvulsive status epilepticus, 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

agnosis of NCSE and that the observation of compression of the EEG time base is effective for detecting evolution of the ictal pattern over time (5).
The standard treatment for anti-NMDAR encephalitis includes various immunotherapies in addition to tumor removal (1-3). Corticosteroids, plasmapheresis and intravenous 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

Table. Three Cases of Refractory NCSE with Anti-NMDAR Encephalitis

Refer- ence	Age sex	Tumor	EEG findings	Anti-epileptic drugs	Therapy of encephalitis	Duration of status epilepticus	Effective therapy
4	35F	Ovarian teratoma	Cyclical pattern of moderate to high voltage, generalized, anteriorly biased 2 Hz alternating with 5-6 Hz sharp wave activity	PHT, VPA, LEV, BZD Propofol Pentobarbital	IVIg, RTX, CyC Tumor removal	6 months	Tumor removal
5	19F	Mediastinal teratoma	Continuous generalized rhythmic delta activity that evolved into ictal pattern over time	PHT, VPA, LEV, BZD, CBZ, PB, Felbamate Propofol Pentobarbital	Steroid, PE, RTX Tumor removal	6 weeks	Felbamate
Our case	48F	None	Generalized, frontotemporal predominant, rhythmic slow delta activity that evolved into ictal pattern	PB, LEV, TPM, LTG Midazolam Propofol	Steroid, IVIg, PE RTX, CyC	3 months	RTX, CyC

EEG: electroencephalogram, PHT: phenytoin, VPA: valproic acid, LEV: levetiracetam, BZD: benzodiazepine, CBZ: carbamazepine, PB: phenobarbital, TPM: topiramate, LTG: lamotrigine, IVIg: intravenous immunoglobulin, RTX: rituximab, CyC: cyclophosphamide, PE: plasma exchange

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 unresponsive 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).

Acknowledgement

The authors thank Dr. Maarten Titulae and Prof. Josep Dalmau for measuring the anti-NMDA receptor antibodies in the patient's CSF and serum, Dr. Jun Shimizu for measuring the antibodies to Hu, Yo, Ri, amphiphysin, Ma2 and recoverin antigens and Dr. Osamu Watanabe for measuring the antibodies to voltage-gated potassium channel (VGKC).

References

1. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 7: 1091-1098, 2008.
2. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 10: 63-

- 74, 2011.
3. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* **12**: 157-165, 2013.
4. Johnson N, Henry C, Fessler AJ, Dalmau J. Anti-NMDA receptor encephalitis causing prolonged nonconvulsive status epilepticus. *Neurology* **75**: 1480-1482, 2010.
5. Kirkpatrick MP, Clarke CD, Sonmez Turk HH, Abou-Khalil B. Rhythmic delta activity represents a form of nonconvulsive status epilepticus in anti-NMDA receptor antibody encephalitis. *Epilepsy Behav* **20**: 392-394, 2011.
6. Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology* **70**: 504-511, 2008.
7. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* **79**: 1094-1100, 2012.
8. Ishiura H, Matsuda S, Higashihara M, et al. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. *Neurology* **71**: 1921-1923, 2008.
9. Ikeguchi R, Shibuya K, Akiyama S, et al. Rituximab used successfully in the treatment of anti-NMDA receptor encephalitis. *Intern Med* **51**: 1585-1589, 2012.
10. Kashyape P, Taylor E, Ng J, Krishnakumar D, Kirkham F, Whitney A. Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with Cyclophosphamide: the need for early aggressive immunotherapy in tumour negative paediatric patients. *Eur J Paediatr Neurol* **16**: 74-78, 2012.
11. Gabilondo I, Saiz A, Galán L, et al. Analysis of relapses in anti-NMDAR encephalitis. *Neurology* **77**: 996-999, 2011.
12. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* **133**: 1655-1667, 2010.