Long-term and Strong Immunotherapy to Treat Anti-N-Methyl-D-Aspartate Receptor Encephalitis with Refractory Status Epilepticus

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Abstract-

Background: Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) encephalitis is responsive to immunotherapy and removal of tumor, but there is no consensus in the treatment of severe anti-NMDAR encephalitis with prolonged refractory status epilepticus (SE).

Case Report: A 17-year-old girl presented as acute psychosis, refractory seizures, hyperkinesia, autonomic instability, and soon progressed to a dissociative state of coma. Anti-NMDAR antibodies were positive in serum and CSF. When most of the symptoms were alleviated after repeated one-by-one immunotherapy during the first four months, the patient still remained in a coma with frequent seizures despite treatment with five different anti-epileptic drugs. We then proposed a three-combined immunotherapy of high-dose steroid, intravenous immunoglobulin and rituximab. After such treatment, her SE was soon resolved and this patient regained her consciousness before resection of ovarian teratoma. Although she had suffered from a prolonged period of refractory SE and coma for six months, she still had good recovery from encephalitis after a long-term immunotherapy.

Conclusion: A strong and long-term course of immunotherapy is necessary in treating severe refractory anti-NMDAR encephalitis. If traditional step-by-step way of immunotherapy is not strong enough to rapidly cure severe anti-NMDAR encephalitis, combined immunosuppressive agents can be considered to shorten the clinical course.

Key Words: Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) encephalitis, Immunotherapy, Refractory status epilepticus

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INTRODUCTION

Anti-N-Methyl-D-Aspartate receptor (anti-NMDAR) encephalitis, an autoimmune disease with antibodies against the NR1/NR2B heteromer of the N-Methyl-D-Aspartate receptor, was identified in 2005. It is

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characterized by acute mental status change, seizures, autonomic instability, hyperkinesia and presence of teratoma[1]. The treatment includes immunotherapy and tumor resection. The first-line immunosuppressive treatment included IVIg, pulse steroid therapy and plasma exchange. Rituximab and cyclophosphamide are considered as the second-line immunotherapy[1]. Based on the previous reports, half of the patients with anti-NMDAR encephalitis had response to the first-line immunotherapy. In patients refractory to the first-line immunotherapy, subsequent treatment with the second-line immunotherapy may improve clinical outcome[2]. Although anti-NMDAR encephalitis has been generally regarded as one of the immunoresponsive disorders, 22% of patients still had poor functional outcome despite the first-line and the second-line immunotherapy[2]. One of the current problems is no guideline to tell us about the most appropriate immunosuppressive strategy according to different severity of disease. Those immunosuppressive drugs were often used one-by-one, but there has been no consensus if those drugs should be simultaneously used. There is also no knowing how many times those patients should be treated. Here we would like to report the course of immunotherapy in a patient who had been repeatedly treated with immunosuppressive drugs for several months and finally had a good recovery from severe anti-NMDAR encephalitis. We shall also briefly discuss the effectiveness of combined immunotherapy in treating such a recalcitrant anti-NMDAR encephalitis.

CASE REPORT

On October 8, 2014, a 17-year-old girl, JP, was admitted to our neurology ward due to acute delirium. This previously healthy girl began suffering from intermittent dizziness and transient loss of consciousness 10 days before admission. These symptoms occurred more frequently and then she behaved rather oddly. JP soon became disoriented and unable to cope with daily activities. Three days before admission, she had fever. Neither convulsion nor involuntary movement was noted before admission.

Her consciousness deteriorated so rapidly that she had little response to external stimuli within 2 days. The results of brain magnetic resonance imaging, routine laboratory examinations and autoimmune profile were all unremarkable. Analysis of cerebrospinal fluid showed WBC count=0, glucose=93 mg/dL, and protein=17 mg/dL. But, her IgG index was as high as 2.26. Electroencephalography (EEG) revealed trains of epileptic discharges consisting of fast activity, followed by 4-6 Hz sharp waves arising from the right temporal area and often spreading to the other hemisphere. She was then diagnosed as complex partial status epilepticus (SE), for which she was treated with phenytoin, levetiracetam and clonazepam.

JP soon lapsed into a dissociative state of coma, often resisting eye opening but with little response to painful stimuli. Besides, she had involuntary movements including oro-lingual-facial dyskinesia, oculogyric crisis, elaborate motions of the arms and legs, dystonia, and opisthotonus, which occurred simultaneously or alternatively with motor seizures. At that time, she also had fever, tachycardia, and hyper-salivation.

Based on the constellation of her symptoms, we diagnosed her illness as anti-NMDAR encephalitis. Anti-NMDAR antibodies were positive in serum and CSF. For her SE, she had to be admitted to intensive care unit (ICU) to be intubated and treated with sedative agents, including midazolam, propofol and thiamylal. However, she still had refractory seizures despite so many anti-epileptic drugs (AEDs) and sedative agents. For her encephalitis, we started immune modulation therapy on October 20. Details of the course of immunotherapy are listed in Table 1. To investigate whether she had ovarian tumor or not, she was examined by computer tomography (CT) of the pelvic cavity twice: the first one on October 23 and the second one on December 2. However, teratoma was not found in either CT examination.

After being treated with first- and second-line immunotherapy from October 20 to December 22, JP had less involuntary movements (see comments on Table 1). However, there was little improvement in SE. Although she was treated with maximum dose of phenytoin, phenobarbital, levetiracetam, topiramate and pregabalin, monitoring with video EEG still revealed frequent non-convulsive SE. The only way to stop her seizures was using sedative agents; and any attempt to wean her from sedation often resulted in motor seizures.

There was an incidental improvement in EEG between

Table 1. Details of the course of immunotherapy.

Date	Drugs (dose)	Comments
2014/10/20 -10/23	Methylprednisolone (500mg/day)	No clinical improvement
2014/10/24 -10/29	IVIg (0.4 mg/kg/day)	No clinical improvement
2014/11/01 -11/05	Methylprednisolone (500mg/day)	No clinical improvement
2014/11/06, 13, 20, 27	Rituximab (375mg/m^2)	No clinical improvement
2014/12/08 -12/12	Methylprednisolone (500mg/day)	Less involuntary movements
2014/12/18 -12/22	IVIg (0.4 mg/kg/day)	Less involuntary movements
2015/01/05, 12, 19	Rituximab (375mg/m^2)	No more significant change
2015/01/16 -01/17	Methylprednisolone (500mg/day)	
2015/01/18 -01/20	Methylprednisolone (1000mg/day)	
2015/01/16 -01/20	IVIg (0.4 mg/kg/day)	Transient improvement in EEG*
2015/02/05 -02/10	Methylprednisolone (1000mg/day)	Weaning from sedatives since 2/17
2015/03/16	Rituximab (375mg/m^2)	
2015/03/16 -03/19	Methylprednisolone (500mg/day)	
2015/03/16 -03/20	IVIg 0.4 (mg/kg/day)	Regained consciousness on 3/27

*EEG: electroencephalography

January 16 and 20, 2015. During those days, JP was simultaneously treated with steroid pulse therapy, IVIg, and rituximab. There was a significant but temporary improvement in EEG, but clinically JP remained in a coma. Due to this inspiring EEG finding, we proposed to treat her with three-combined immunotherapy again from March 16 to 20, when she was infection-free.

On March 22, the third abdominal CT scan revealed a teratoma in the right ovary, for which oopherectomy was scheduled on March 28. Surprisingly she regained consciousness in the night of March 27, which occurred one week after three-combined immunotherapy. She dramatically regained her consciousness just one night before operation.

Thereafter, JP recovered rapidly. Although she had lost her consciousness for six months, she could recognize her family soon after she regained her consciousness. Despite lying on bed for half year, she soon recovered her motor function within 2-3 weeks after awakening. Because there was no recurrence of seizure, all the AEDs were tapered off within two months. When she was discharged on May 8, 2015, she behaved as a normal person. We have observed this girl for one year, and she is good without any sequelae of encephalitis.

DISCUSSION

There are few reports in treating patients with severe anti-NMDAR encephalitis. If the patients were refractory to the first-line immunotherapy, Dalmau et al recommended rituximab and cyclophosphamide as the second-line immunotherapy[1]. Kadoya and his colleague had successfully treated a refractory SE of anti-NMDAR encephalitis by using such dual immunotherapy[3]. However, administration of those immunosuppressive drugs is no guarantee of successful treatment in severe case. Thomas et al had presented a patient with extremely severe refractory anti-NMDAR encephalitis who died after 25-month hospitalization despite the tumor resection and several cycles of immunotherapy[4]. That patient had been repeatedly treated with the first-line or the second-line drugs, but had never been treated with combined immunotherapy. Actually, there is no knowing what the most effective therapy would be in treating such refractory patients. Tumor resection or prophylactic oophorectomy has been considered another optional treatment which may

provide benefit in managing patients with refractory anti-NMDAR encephalitis[5]. There were some reports saying patients with prolonged SE caused by anti-NMDAR encephalitis could recover after tumor resection[6,7]. However, the importance of immunotherapy in treating refractory anti-NMDAR encephalitis was seldom discussed.

This case report clearly showed the effectiveness of immunotherapy in treating refractory anti-NMDAR encephalitis because this patient regained her consciousness before resection of teratoma. It implies that not only the power of immunotherapy must be strong enough to overcome the inflammatory process of encephalitis when we are to use immunosuppressive drugs to treat patients with refractory anti-NMDAR encephalitis, but also the duration of therapy must be long enough. As in this case, immunotherapy was continued as long as the disease was still active. The remaining question was how many drugs should be used together to get a powerful immunosuppression.

During the first four months, we repeatedly used the first-line drugs followed by the second-line drugs. Such one-by-one therapeutic way seemed unable to provide enough power to cease the inflammation, even though we repeated several cycles of immunotherapy. We incidentally found improvement in EEG when three kinds of immunosuppressive drugs were used together. Based on this inspiring electrophysiological finding, we supposed three-combined immunotherapy is more powerful than three separate immunosuppressive drugs. We therefore proposed a three-combined immunotherapy of pulse steroid therapy, IVIg and rituximab to treat this patient. Patient soon regained her consciousness just one week after such treatment. This dramatic effect gave us an answer to the second question: the power of immunotherapy should be strong enough to cease the inflammatory process of the disease.

Prior to this patient, we had taken care of a 24-year-old woman who also had severe anti-NMDAR encephalitis with refractory seizures (not published). The disease severity was similar to JP, but she only accepted one course of pulse steroid therapy and IVIg, one course of rituximab and resection of bilateral ovary during the early stage of the disease. She then stayed in hospital for half year, and remained in a minimally conscious state when she was discharged. According to the limited experience in taking care of patients with severe anti-NMDAR encephalitis, we can learn that a successful immunotherapy depends on two important factors: enough duration and enough strength of therapy.

Someone may argue that full recovering from anti-NMDAR encephalitis could be the nature course of this disease. There were some reports about spontaneous recovery from anti-NMDAR encephalitis with prolonged SE without tumor resection or immunotherapy. However, those patients had an extremely long clinical course and hospitalization[8]. All things considered, we can agree to the argument that immunotherapy may alleviate the severity of symptoms or shorten the clinical course, but not change the prognosis of the disease. Because there is no biomarker to predict the outcome of patients, this argument remains a matter for debate. According to the dramatic therapeutic effect after JP accepted three-combined immunotherapy, we still propose a strong immunotherapy to shorten the clinical course of severe anti-NMDAR encephalitis.

It is generally accepted that the duration of SE determines the prognosis in patients with epilepsy. “The longer duration, the worse prognosis”[9]. But it seems not the case in patients with anti-NMDAR encephalitis. Patients who had suffered from a long period of refractory SE still could have very good functional outcome. Good prognosis can be seen in those patients with refractory SE due to autoimmune encephalitis[10]. This implies the pathology of the brain and pathophysiology of the seizures in those patients with inflammatory encephalitis should be different from those of epileptic encephalopathy[11]. The refractory seizures of patients with anti-NMDAR encephalitis are provoked by extensive inflammatory process. As shown in this case, SE soon resolved when the inflammation of brain was stopped. For this sake, immunosuppressive drugs should be as important as AEDs in treating refractory SE in patients with severe anti-NMDAR encephalitis. Strong immunosuppressive drugs can reduce the inflammation, so that seizures can be stopped. As to the use of AEDs, the problem of polypharmacy was often encountered. Because their brains often had extensive inflammation in acute stage of encephalitis, patients often had refractory seizures which were almost not responsive to polypharmacy treatment.

"No response, more drugs" is a paradox in using AEDs to treat patients with refractory SE. Actually, we did not know how many drugs should be used to prevent secondary brain damage induced by prolonged SE, and this issue was also rarely discussed[12,13].

In conclusion, this case report puts emphasis on the strong immunotherapy to treat patients of severe anti-NMDAR encephalitis with refractory SE. The duration and the strength of immunotherapy are two important determinants of a successful treatment. We proposed a three-combined immunotherapy which seemed to be an effective treatment to shorten the clinical course. How to use multiple AEDs remains an issue to be investigated.

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