Early immunotherapy in cryptogenic new onset refractory status epilepticus (NORSE), a case series

¹Do-Hyung Kim *MD*, ²Tae-Won Yang *MD*, ¹Oh-Young Kwon *MD PhD*, ¹Young-Soo Kim *MD PhD*

¹Department of Neurology, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine; ²Department of Neurology, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Republic of Korea

Abstract

To date, there are no clear guidelines for treatment of cryptogenic new onset refractory status epilepticus (NORSE) syndrome. Immunotherapy was effective for some patients, but the initiation time was often somewhat late. We experienced two cryptogenic NORSE syndrome patients with favorable outcomes with early immunotherapy. A 59 years old male patient and a 58 years old female patient visited our hospital in status epilepticus, who were later diagnosed as cryptogenic NORSE after full evaluation. Since seizures were not controlled by two or more antiepileptic drugs in both patients, immunotherapy began on the fifth day of hospitalization. There was improvement on EEG and clinical symptoms, one or two days after initiation of immunotherapy. Early diagnosis of NORSE and early immunotherapy may result in favorable outcome.

Keywords: New onset refractory status epilepticus (NORSE), status epilepticus, epilepsy, immunotherapy

INTRODUCTION

A small number of people without a history of epilepsy or neurological disease visit emergency room (ER) in lifetime first status epilepticus (SE) condition, where seizures are not controlled by two or more antiepileptic drugs (AEDs).¹ Such cases are called new onset refractory status epilepticus (NORSE), and NORSE can be fatal or can result in severe neurological sequelae.² The pathogenesis of NORSE was previously unknown, but currently the etiology of some of the NORSE patients are now known. The causes are non-paraneoplastic autoimmune in 19%, paraneoplastic 18%, and infection related 8%. Fifty-two percent of NORSE patients are cryptogenic.³ An optimal management strategy for NORSE is still uncertain. Treatment for the patients with NORSE is variable from one case to another, although case series have reported that various immunotherapies are effective for seizure control with favorable outcome.^{2,4-6} Even though decision is often made to try immunotherapy for NORSE, it is common to delay the initiation timing of immunotherapy because of the use of various AEDs to control the SE.2,4-6 We report two cryptogenic NORSE patients in whom the immunotherapy were commenced within the first week of illness. The SE was well controlled and the outcome of the patients was good.

CASE REPORTS

Patient 1

A 59-year-old male patient with no known medical illness visited our hospital with first onset generalized tonic-clonic (GTC) seizure. Post-ictally the patient was confused. Laboratory findings, including the cerebrospinal fluid (CSF) examination in the emergency room (ER), were normal. Brain MRI/MRA showed an increased perfusion on the left frontal area (Figure 1), with no focal lesions detected that could trigger the seizure. An initial EEG on the same day showed three electrographic seizures in the frontopolar area of the left hemisphere. (Figure 2 (A), (B)) Loading dose of levetiracetam was sequentially administered after an injection of diazepam, lorazepam, and a loading dose of valproic acid. Although the patient's consciousness seem slightly improved, a follow-up EEG on his third day of hospitalization revealed two episodes of electrographic seizure in the same area. The patient's consciousness remained clouded with impaired memory. The EEG examination on

Address correspondence to: Young-Soo Kim, MD, PhD, Department of Neurology, Gyeongsang National University College of Medicine, 79, Gangnam-ro, Jinju-si, Gyeonsangnam-do, 52727, Republic of Korea. Tel. +82-55-750-8077, E-mail: youngsookim0127@gmail.com



Figure 1. MRI findings of NORSE patient 1. Perfusion was increased at left frontal area on Arterial Spin Labeling (ASL) images (A), whereas no remarkable findings were observed on T2 FLAIR images (B), Gadolinium enhanced T1 images (C), and Diffusion Weighted Images (D).

fourth day of hospitalization also showed ictal discharges, so we diagnosed NORSE. On his fifth day of admission, we began immunotherapies by intravenous immunoglobulin (IVIG) (0.4g/kg) and high dose intravenous methylprednisolone (1g/day) for five days. On the second day of immunotherapies, EEG changed to occasional short bursts of rhythmic delta slow waves of medium amplitude on the bilateral frontal area without electrographic ictal discharges. (Figure 2 (B), (C)) Clinically the patient gradual improvement in his conscious level and memory, without further clinical seizure. When the immunotherapies were completed, we observed that the patient has fully recovered in conscious level and memory. A follow-up EEG performed one month after the completion of immunotherapies was normal. (Figure 2 (D), (F)) The antibody panels for paraneoplastic (Hu, Yo, Ri, Ma2, CV2/CRMP5, amphyphysin, recoverin, SOX1, titin) and autoimmune encephalitis (NMDAR, AMPA1, AMPA2, LGI1, CASPR2, GABA-B) two weeks after the completion of immunotherapies were all negative.

Patient 2

A 58-year-old female patient visited our hospital for treatment of first onset seizure. She has been taking antiplatelet and antihypertensive medications for three years, and she was otherwise healthy. A total of six GTC type seizures were observed, and her mental status did not recover after the convulsive events. We initially administered diazepam, lorazepam, and a loading dose of levetiracetam. Routine laboratory findings including CSF examination in the ER were normal, and no focal lesion in brain MRI/MRA was detected. An initial EEG revealed two subclinical electrographic seizures in the frontotemporal area of the left hemisphere. (Figure 3 (A), (B)) After the EEG, the patient received a loading dose of fosPHT. We also treated her empirically with acyclovir and dexamethasone, because we could not exclude the possibility of viral encephalitis. A followup EEG during her third day of hospitalization revealed no improvement and her mental status was deeply drowsy to stupor state. Rather than administering additional AEDs, we gave her immunotherapies, as we concluded that she has NORSE. We substituted dexamethasone with high dose intravenous methylprednisolone (1g/day) on her fourth day of hospitalization, and IVIG (0.4g/ kg) was added on the fifth day of hospitalization. On the second day of immunotherapy, EEG had improved to frequent bursts of rhythmic or semirhythmic delta slow waves of medium amplitude on bilateral hemisphere without any electrographic seizure discharges. (Figure 3 (C), (D)) Level of consciousness had gradually



Figure 2. EEG findings of NORSE patient 1. The EEG was recorded with the filter set to 1-70 Hz using a notch filter of 60 Hz. Sensitivity is 200uVp-p in all pictures. Initial EEG showed repetitive rhythmic alpha activities at Fp1 on average montage (A), and bipolar montage (B). Follow up EEG after immunotherapy showed short bursts of rhythmic delta slow waves of medium amplitude at the bilateral frontal area on average montage (C) and bipolar montage (D). Follow up EEG 1 month later was within normal limits on average montage (E) and bipolar montage (F).

improved from deep drowsy state to being alert, and the patient did not have focal neurologic deficit other than occasional headaches and fatigue. One month after completion of immunotherapies, EEG showed mild diffuse slow waves, and three months later EEG finding was within normal limit. (Figure 3 (E), (F)) The results of antibody panels for paraneoplastic (Hu, Yo, Ri, Ma2, CV2/ CRMP5, amphiphysin, recoverin, SOX1, titin) and autoimmune encephalitis (NMDAR, AMPA1, AMPA2, LGI1, CASPR2, GABA-B) one month after completion of immunotherapies were normal.

DISCUSSION

Wilder-Smith *et al.* in 2005 were the first to report seven patients who were previous healthy, presenting with refractory SE without

underlying cause, and named the condition NORSE syndrome.⁶ Gaspard *et al.* in 2015 that retrospectively reviewed the records from 13 academic medical centers over six years and reported 130 cases of NORSE.³ They performed an extensive evaluation and analysis of the causes of NORSE, and found the causes could be confirmed for 48% of patients (19% autoimmune encephalitis, 18% paraneoplastic encephalitis). However, in 67 cases (52%), the causes remained unknown despite extensive investigation. Such cases were called "cryptogenic NORSE" or "NORSE of unknown etiology".¹

Various investigators have used different immunotherapies to manage patients with cryptogenic NORSE, when AED fails to control the seizure and the patients do not recover from their neurological deficits, with some positive



Figure 3. EEG findings of NORSE patient 2. The EEG was recorded with the filter set to 1-70 Hz using a notch filter of 60 Hz. Sensitivity is 200uVp-p in all pictures. Initial EEG showed repetitive alpha to beta activities at Fp1, then metamorphosis to the semi-rhythmic delta to theta slow waves on the same area with propagation to the frontal area on the same hemisphere (F3/F7/F9) on average montage (A) and bipolar montage (B). Follow up EEG after immunotherapy showed bursts of rhythmic or semirhythmic delta slow waves at the bilateral hemisphere on average montage (C) and bipolar montage (D). Follow up EEG 3 months later was within normal limits on average montage (E) and bipolar montage (F).

results.¹ Therapies such as steroid/ IVIG/ketogenic diet/plasmapheresis/hypothermia treatments have been tried, other than AEDs.^{2,4-6} Effectiveness of these treatments have been reported to be variable, with favorable outcome observed in 30-67%. However these findings were from small case series, therefore optimal management for NORSE can be said to be still uncertain.¹

In the reported cases, the timing of the initiation of the immunotherapies varies from one case to another, and it is difficult to identify the timing of the commencement of immunotherapy for majority of cases. Among the identified cases of early initiation of immunotherapy, in the case by Li *et al.*, the immunotherapy was plasma exchange which was given at the fifth day after the onset of symptoms of SE.⁴ The seizures did not recur after plasma exchange, and the outcome was moderately impaired memory and complex partial seizures. In addition to this case, there were cases that steroid was used in the twelfth day after the onset of symptoms of SE, with IVIG and steroid administered together two weeks after the symptom onset as reported by Gall *et al.* and Li *et al.*^{2,4} The outcome of Gall's case was good with no deficits, and seizures were controlled on azathioprine and AEDs. However the outcome was not favorable in Li's case. Correlation between early initiation of immunotherapy and outcome is hard to be certain due to small number of cases. More case series or comprehensive study is needed.

The main reason why immunotherapies are often delayed is that physicians often delay the use of immunotherapy until they fail midazolam or propofol, when two or more AEDs are not effective in arresting the SE.^{24,5} We began immunotherapies for the two patients with NORSE in a relatively early stage, within five days after observing symptoms of the onset of SE, rather than adding other 3rd line AEDs, or use general anesthesia after clinically diagnosing them as NORSE.

The initiation of immunotherapies for the two patients in this report was earlier than that in many other reported studies. This was despite the fact that it was impossible to identify the definitive etiology cause of NORSE when we initiate the immunotherapies. It took between two weeks and a month to receive the result of the antibody panels for paraneoplastic and autoimmune encephalitis, although it may be faster among some laboratories.

We conclude that the patient who visits a hospital for continued epilepsy can be diagnosed with possible NORSE when refractory SE occurs, where MRI, EEG, CSF study, and routine lab examinations do not point to a definitive cause, even though some of laboratory tests are still not available. Our two patients demonstrate the potential benefit of early immunotherapy in cryptogenic NORSE patients in this situation. Future systemic prospective investigations are needed to determine the appropriate types of immunotherapies and their timing.

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