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Case Report NEUROLOGY

Anti-N-methyl D-aspartate receptor encephalitis presenting with the new-onset refractory status epilepticus

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ABSTRACT

New-onset refractory status epilepticus (NORSE) is a rare entity referring refractory status epilepticus (SE) in a patient without a history of epilepsy or an apparent cause. Herein, we report on a 31-year-old young female of anti-N-methyl D-aspartate (NMDA) receptor encephalitis admitted with NORSE. Her complaints began a week ago with a fever, meaningless movements, restlessness, and talking to herself. She had a history of operation for ovarian teratoma 10 years ago. Electrocardiography, hemogram, biochemistry, and neuroimaging were normal. Due to recurrent seizures despite intravenous diazepam infusions, phenytoin infusion was introduced, reducing the duration and frequency of seizures. Electroencephalogram (EEG) revealed a generalized slow background activity with low voltage and delta waves in left hemisphere derivatives without any epileptiform discharge. Autoimmune encephalitis panel revealed a positive anti-NMDAR receptor antibody. Intravenous immunoglobulins were given for 5 days. She was improved clinically and did not have a recurrent seizure. The history of our case emphasizes the importance of EEG and CSF antibody tests to reach the underlying etiology in patients presenting with refractory SE and neuropsychiatric symptoms of an unknown cause. Application of a proper treatment promptly with this approach could prevent the potential morbidity and mortality in these patients.

Keywords: Anti-N-methyl d-aspartate receptor encephalitis; anti-N-methyl D-aspartate receptor encephalitis; cerebrospinal fluid; electroencephalogram; new-onset refractory status epilepticus; NORSE.

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The new-onset refractory status epilepticus (NORSE) is a rare clinical entity that was first defined by Wilder-Smith et al. to describe the cases with acute refractory status epilepticus (SE) without a clear structural, toxic, or metabolic cause in a patient without a history of active epilepsy [1–3]. It is thought to have a similar etiopathogenesis with febrile infection-related epilepsy syndrome [4, 5]. The description of cryptogenic NORSE requires the development of new-onset-resistant SE in previously healthy individuals, resistance to traditional antiepileptic therapy, and absence of a determined etiology during the initial examination. If the underlying etiology for SE could be revealed, the determined disease is begun to use as the specific diagnosis for these patients. In previous case series, various etiologies have been defined up to date, which could be classified as inflammatory or autoimmune encephalitis, genetic disorders, toxic causes, and infectious encephalitis [6–8]. Inflammatory or autoimmune encephalitis is the leading causes in approximately 40% of NORSE cases, whereas any etiology could not be revealed in more than half of these patients.

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Antibodies in autoimmune encephalitis target either the intracellular or the cell-surface antigens. The types of antibodies are associated with different clinical features, cancer associations, and immune therapy responsiveness. Antibodies against intracellular nuclear and cytoplasmic proteins named onconeuronal antibodies (e.g., anti-Hu, anti-Ma, anti-Ri), generally accompany to the malignancies. Patients producing these antibodies respond poorly to immunotherapy, but the treatment of underlying malignancy could result in neurological improvement. Antibodies against neuronal cell-surface antigens target an extracellular epitope and their corresponding antigens, often synaptic receptors or components of synaptic protein complexes. Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) antibodies are the most common one which followed by antibodies against leucine-rich glioma inactivated-1, contactin-associated protein-like 2, and anti-voltage-gated potassium channel (VGKC). Encephalitis associated with anti-NMDAR antibodies is caused by immune-reactivity against the NR1 subunit of the NMDAR. Autoantibodies are produced against the nerve surface or synaptic antigens in anti-NMDAR encephalitis. Hyperactivation of NMDAR leads to acute neuronal death and chronic neurodegeneration, whereas hypoactivation of NMDAR plays an essential role in the occurrence of psychiatric symptoms [9–12]. Anti-NMDAR encephalitis may present with fever, short-term memory loss, neuropsychiatric symptoms, and respiratory distress in the prodromal period, mainly affecting young women. Herein, we present the history, results of laboratory investigations, and clinical follow-up of a young NORSE patient who was diagnosed with anti-NMDAR encephalitis.

CASE REPORT

A 31-year-old female patient was admitted to our emergency room (ER) with a generalized tonic-clonic seizure. A fever, meaningless movements, restlessness, and self-talk complaints had started a week ago in her medical history. She had a history of surgery for ovarian teratoma 10 years ago. There was no history of drug use. Two polymerase chain reaction (PCR) tests for novel coronavirus disease-2019 performed within the last week were negative. During the initial neurological examination in our ER, she was in the postictal period; her general condition was moderate, her consciousness was drowsy, and cooperation was limited. There was no neck stiffness, pupils equally round, and reactive to light. There was not any facial asymmetry. Examination of other cranial nerves was normal. Spontaneous motor movements were observed in all extremities. Plantar reflexes were flexor bilaterally. Vital findings were stable.

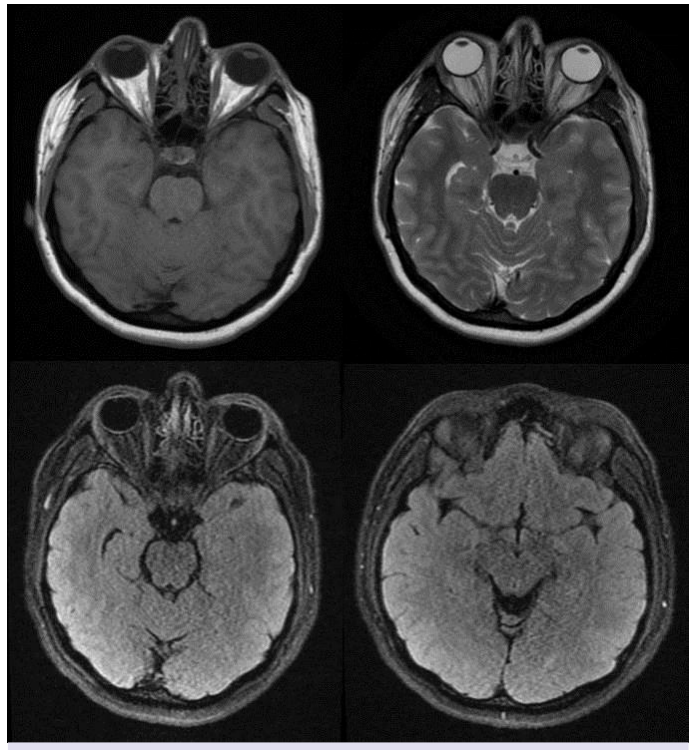

Figure 1. Brain MRI of the patient was normal (Upper row: Axial T2-weighted sequences, Lower row: Axial FLAIR sequences).
MRI: Magnetic resonance imaging; FLAIR: Fluid-attenuated inversion recovery.

Electrocardiography was regular with normal sinus rhythm. There was not any gross abnormality in hemogram and serum biochemistry tests. Lactate level was slightly elevated to 1.74 mmol/L (0.5-1.6 mmol/L). Brain computerized tomography (CT), magnetic resonance imaging (MRI), and MRI-venography were normal (Fig. 1).

There was not any sign of pneumonia on thorax CT. Due to recurrent seizures despite intravenous diazepam infusions in our ER, phenytoin infusion was introduced. A partial reduction in frequency and duration of the seizures were obtained after phenytoin infusion. Then, she was hospitalized in our intensive care unit. Intravenous phenytoin was maintained with the dosage of 100 mg t.i.d.

Electroencephalogram (EEG) revealed a generalized slow background activity with low voltage that was observed throughout the whole trace without any accompanying epileptiform discharge. Delta waves were observed in the left frontotemporal and central areas (Fig. 2).

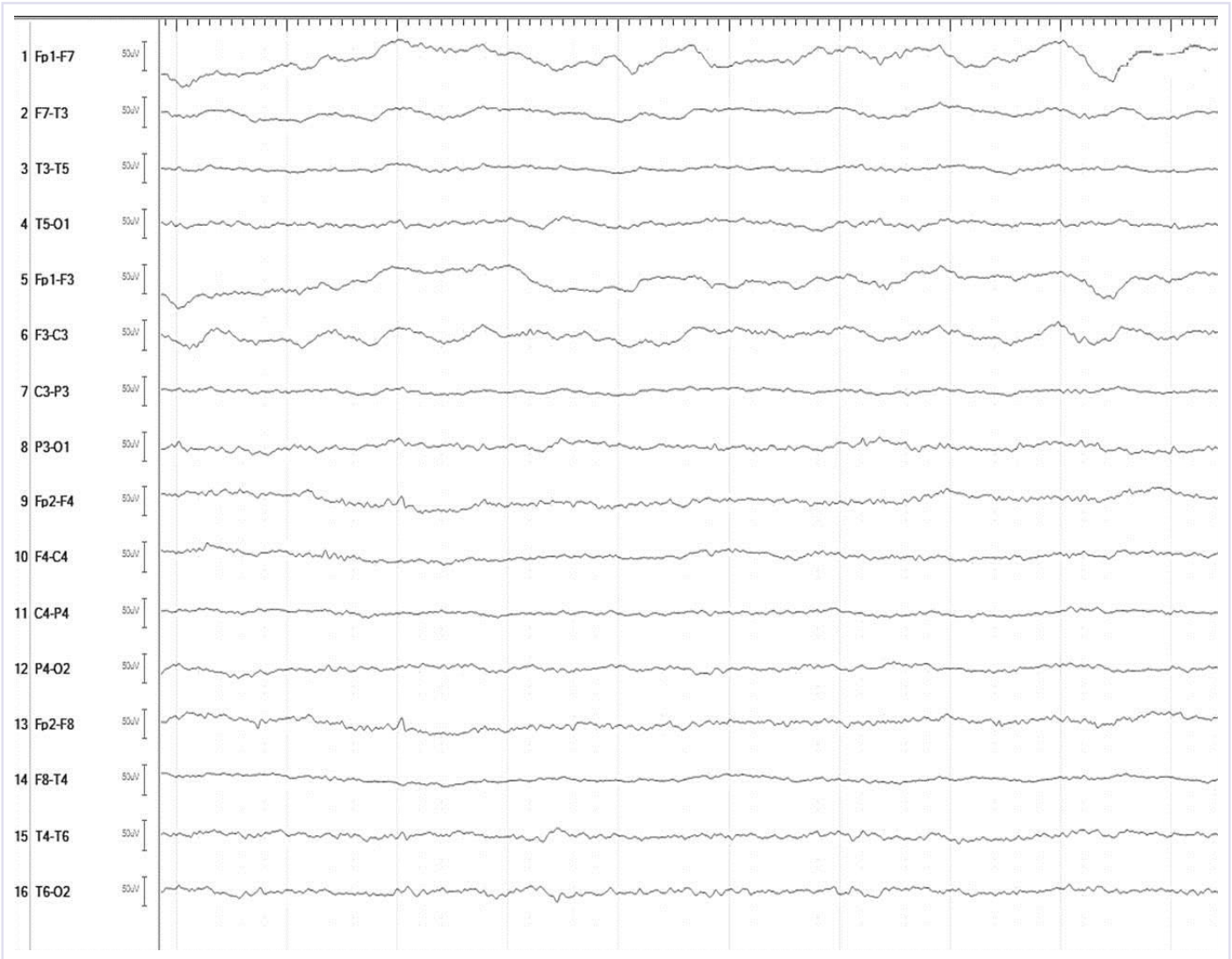

FIGURE 2. EEG trace shown in the longitudinal bipolar montage; sensitivity: 7 μV; low-frequency filter: 0.3 Hz; high-frequency filter: 35 Hz. Speed: 10 s/page. A generalized slow background activity with low voltage and delta waves was observed in left hemisphere derivatives, more prominent in the left frontotemporal and central areas without any epileptiform discharge.

EEG: Electroencephalogram.

During her follow-up, dexmedetomidine infusion was started to decrease her agitation. Opening pressure (17 cm H_2O) was normal during the lumbar puncture. Leukocyte count was 10/mm^3, erythrocyte count was 10/mm^3, and protein level was 29 mg/dl in cerebrospinal fluid (CSF). Prophylactic ceftriaxone (2×2 g), vancomycin (2×1 g), and acyclovir (3×750 mg) were started upon the recommendations of our infectious disease department. Haloperidol and chlorpromazine treatments were initiated after psychiatry consultation requested for the consideration of her persistent agitation. Lorazepam was added during the follow-up. Extensive panel tests for meningitis were negative. CSF-PCR for tuberculosis, Gram's stain of sputum, acid–fast bacilli scan, venereal disease research laboratory-rapid, plasma reagin, treponema pallidum hemagglutination, Rose Bengal test for Brucella results were all negative. Serum ammonia level (77.7 μmol/L) was normal. Upon the persistence of her agitation, mirtazapine and quetiapine were added.

Autoimmune encephalitis panel assessed with immunofluorescence assay revealed NMDAR receptor antibodies in CSF. Intravenous immunoglobulins (IVIG) were administered as 25 g per day. After IVIG therapy for 5 days, her seizures were ceased. She was

conscious and partially cooperative at the end of the 2nd week and was discharged. During the outpatient clinic follow-up at the end of 6 weeks, the patient did not report any recurrent seizures, and her neurological examination was completely normal. Rituximab treatment was introduced for long-term immunomodulation.

DISCUSSION

Anti-NMDAR encephalitis could present with various neuropsychiatric symptoms and resistant epileptic seizures. Seizures generally tend to be generalized tonic-clonic type and refractory to the initial treatments. Conventional CSF analyses, brain MRI, or EEG generally did not give any guiding result in these patients. Non-specific hyperintense signals might infrequently be observed in the cerebral cortex, medial temporal region, or corpus callosum in fluid-attenuated inversion recovery (FLAIR) sequences of MRI in some patients with anti-NMDAR encephalitis. There is not any specific EEG finding for these cases. A generalized slowing with or without focal epileptic activity is the most commonly reported abnormality in previous case series. Asymmetrical or focal slowing, as in our case, a generalized epileptiform activity or extreme delta brushes were also reported in some instances [13, 14]. Therefore, the definitive diagnosis of anti-NMDAR encephalitis could only be made by detecting the autoantibodies in suspected cases. The sensitivity of anti-NMDAR antibody testing is higher in CSF than in serum, and anti-NMDAR antibody testing in CSF samples is more sensitive than serum samples. The patients with a poor outcome or having a teratoma have higher antibody titers than the patients with a good outcome or having no tumor [15].

Previous case series indicated that early aggressive treatments were associated with better functional outcomes and fewer relapses in patients with anti-NMDAR encephalitis [1, 16, 17]. Immunotherapy and surgery, if there is an underlying tumor, are the main management strategies. Validated immunotherapies include the first-line (steroids, IVIG, and plasmapheresis) and the second-line immunotherapy options (rituximab and cyclophosphamide). Anticonvulsant and antipsychotic treatments were failed to ameliorate the symptoms of our case, whereas the IVIGs resulted in a clear neurologic improvement.

Conclusion

Any significant finding was not found in laboratory investigations and neuroimaging methods performed to detect possible active causes of SE in our patient. Although her laboratory tests, conventional CSF analyses, and neuroimaging were normal, the presence of surgery for an ovarian teratoma in her medical history and a lateralized delta wave activity in her EEG guided us to search for probable autoimmune encephalitis. Therefore, the history of our case emphasizes the importance of performing CSF antibody screening tests for autoimmune encephalitis to reach the underlying etiology in patients with refractory SE and neuropsychiatric symptoms of an unknown cause. Application of a proper treatment promptly with this approach could prevent the potential morbidity and mortality in these patients.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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Authorship Contributions: Concept – MA, SD; Design – MA, TA; Supervision – MA, TA; Fundings – MA; Materials – MA, SD; Data collection and/or processing – MA, SD; Analysis and/or interpretation – MA; Literature review – MA, TA, SD; Writing – MA; Critical review – MA.

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