Introduction

Status epilepticus (SE) is defined as a condition resulting from either initiation of mechanisms leading to prolonged seizure activity and/or failure of mechanisms that terminate seizure activity. New-onset refractory status epilepticus (NORSE) is a clinical presentation that can affect all ages, and can be diagnosed in SE patients without a previous diagnosis of epilepsy or other pre-existing neurological disorders and has no significant acute or active structural, toxic, or metabolic cause. Inflammatory and autoimmune encephalitis including paraneoplastic and sporadic etiologies account for the majority of causes except for cryptogenic etiology. Consequently, the inflammatory mechanism has been considered to be essential in the development of NORSE and immunotherapies have been regarded as an important treatment strategy after anti-seizure medications (ASMs) and anesthetic agents.

Encephalitis encompasses a broad range of pathophysiologic processes that lead to inflammation of the brain parenchyma. The strict diagnosis of encephalitis is established only based on pathological examination of brain tissue; however, tissue is available only in the minority of the victims. Other biological markers of brain inflammation are frequently used, including an elevated cerebrospinal fluid (CSF) leukocyte number and abnormality in neuroimaging. However, patients with NORSE frequently show no abnormality on CSF and neuroimaging especially during the early period of the disease. Despite the presumed inflammatory and autoimmune pathogenesis of NORSE, the lack of reliable biomarkers may hinder the prompt diagnosis and treatment of this potentially life-threatening disease. Interestingly, prior studies illustrated that pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) are markedly increased in patients of refractory repetitive acute seizures. We describe a patient with cryptogenic NORSE and elevated IL-6 levels in both serum and cerebrospinal fluid IL-6 were the only laboratory abnormality during the early evaluation. The patient was successfully treated with tocilizumab, an IL-6 receptor monoclonal antibody.

Case Report

A 24-year-old female visited the emergency department with first onset generalized tonic-clonic (GTC) seizure. She had fever for the past 5 days before the visit and was asymptomatic afterward. She had a history of allergic rhinitis but there was no history of febrile convulsion or epilepsy. She received the first dose of Pfizer-BioNtech COVID-19 vaccine 1 month before the visit, and her mother reported that she complained of non-specific somatic symptoms including fatigue, menstruation abnormality, hair loss, and difficulty in concentration. The patient was admitted for the evaluation of the first
seizure. GTC seizure recurred on the day of admission. She was treated with lorazepam 2 mg and a loading dose of levetiracetam (LEV) 1.5 g with a maintenance dose of 500 mg twice daily along with a loading dose of lacosamide (LCM) 200 mg with a maintenance dose of 100 mg twice daily. Her initial laboratory findings including serum and urine tests and magnetic resonance imaging including gadolinium-enhanced and diffusion-weighted imaging were normal. Two days after hospitalization, she began to suffer from repeated convulsive seizures without recovery of consciousness, thereby requiring an increased dose of LEV (to 1 g twice daily) and LCM (to 200 mg twice daily) with the addition of topiramate (TPM) at 100 mg twice daily. She was transferred to the intensive care unit (ICU) for video-electroencephalogram (EEG) monitoring. EEG showed generalized 2-Hz rhythmic delta activities with extreme delta brush (Fig. 1A), which suggested the diagnosis of autoimmune encephalitis such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. CSF analysis showed normal pressure, normal cell count and normal protein of 44.6 mg/dL with no evidence of infection. With the multiple ASMs, coma therapy using anesthetics, such as midazolam, and thiopental and immunotherapy including steroids (dexamethasone) were initiated from the hospital day 3. EEG showed a continuous burst-suppression pattern (Fig. 1B). Autoimmunity tests (serum and CSF) performed at the hospital on day 3 were all normal including autoimmune synaptic encephalitis antibodies (NMDA, α-amino-3-hy-
Discussion

Our patient was hospitalized for more than 3 months with the diagnosis of NORSE and discharged without further convulsions or other neurologic deficits. After the initial failure of multiple ASMs, she was successfully treated with tocilizumab on two consecutive administrations with a booster infusion with the elevated serum and CSF levels of IL-6, along with other immunotherapy and the ketogenic diet.

Despite the comprehensive investigation, approximately 50% of adult NORSE cases have no identifiable etiology, so they are classified as cryptogenic NORSE.4 Though cryptogenic NORSE is a set of various characteristics such as cognitive impairment, seizures and behavioral changes, the clinical features of NORSE are similar to those of autoimmune etiologies and it is suggested that some cryptogenic NORSE cases may represent autoimmune encephalitis with unidentified autoantibodies.4 It is considered that seizures in NORSE patients with autoimmune or cryptogenic etiologies are mediated by neuroinflammation. Neuroinflammation is the inflammatory response mediated by central nervous system (CNS) resident cells and is regulated by inflammatory mediators such as cytokines and chemokines. Recent studies have shown that seizures trigger the rapid activation of glial cells, thereby leading to increased production of inflammatory mediators to promote an inflammatory process.10

These inflammatory mediators have neuromodulatory effects that lead to changes in neuronal function and connectivity. Consequently, pro-inflammatory cytokines and seizures make worsen each other and induce neuronal hyperexcitability and subsequent seizure susceptibility.9,10

Many cytokines including IL-1β, IL-6, and TNF-α have been implicated in the pathogenesis of epilepsy and NORSE, and prior studies found the most strong and constant relationship between IL-6 and epilepsy.10 Repetitive or prolonged seizures stimulate an inflammatory cascade associated with an increment in IL-6 levels, thereby inducing disruption of the blood-brain barrier and sustaining seizure activity.10,11 It is also reported that there is a strong relationship between elevated serum or CSF IL-6 levels and the severity of seizures.12,13 In our patient, all the serum and CSF studies for the etiologic evaluation for NORSE including autoantibodies showed no abnormality, and we only found that IL-6 levels were elevated in both serum and CSF, which indicates the pivotal role of IL-6 mediated inflammatory response in epileptogenesis of NORSE in our patient.

Tocilizumab was originally used to treat rheumatoid arthritis patients who showed no response to methotrexate or disease-modifying anti-rheumatic drugs. As IL-6 plays an indispensable role in both B- and T-cell differentiation, tocilizumab is regarded as efficient in numerous CNS autoimmune diseases.14 In patients with autoimmune encephalitis, rituximab is frequently recommended along with intravenous steroids and IVIg due to the critical role of neuroinflammation in NORSE.7 Tocilizumab is used as adjunctive immunotherapy in patients who demonstrated failure or unsatisfactory responses to
rituximab. Tocilizumab regimen was usually initiated at a dosage of 5 mg/kg administered for 2 cycles in 1 week intervals and followed by an increase to 8 mg/kg monthly depending on the clinical response. As a potent IL-6 antagonist, we think that tocilizumab may be more effective than rituximab for selected NORSE patients with the demonstrated increase in IL-6 levels, and several reports suggest the role of tocilizumab in the management of intractable NORSE. Nevertheless, it should be noted that early administration of tocilizumab is not yet the standard immunotherapeutic regimens in treating NORSE patients and further studies and consensus are needed to acknowledge tocilizumab as the standard treatments.

Our report had several limitations. First, we assessed serum and CSF IL-6 levels before administration of tocilizumab, but follow-up levels were not evaluated after administration. Although the patient’s clinical symptoms and EEG were improved after tocilizumab therapy, we could not quantify the relationship between cytokine levels and clinical manifestations. In addition, we used several ASMs with high dosages, immunomodulatory therapies other than tocilizumab and even the ketogenic diet for the treatment of NORSE. Apparently, it was hard to evaluate how these treatments influenced the clinical response to the individual treatment modality in our patient. Further prospective controlled studies with additional patients and standardized treatment regimens should be performed to demonstrate the association between IL-6 and NORSE. However, we contemplate that from our patient, it can be suggested that IL-6 may play a principal role in diagnosing and managing this rare but devastating neurologic emergency.

Conflict of Interest

The authors declare that they have no conflicts of interest.

References