Short Communication

Cryptogenic new-onset refractory status epilepticus responded to anti-interleukin-6 treatment

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ARTICLE INFO

Keywords:
Status epilepticus
New-onset refractory status epilepticus
Anti-IL-6 treatment
Tocilizumab

ABSTRACT

Objective: The aim of this case report was to describe a potential anti-interleukin (IL)-6 treatment for cryptogenic new-onset refractory status epilepticus (C-NORSE).

Background: Although an underlying immune-mediated pathogenesis is considered present in some C-NORSE cases, many cases do not respond to classical immunotherapies.

Case report: We describe the case of a 46-year-old woman with C-NORSE who achieved cessation of long-lasting status epilepticus following administration of tocilizumab, an IL-6 receptor-blocking antibody, although the final outcome was poor.

Conclusions: Anti-IL-6 treatment may prove effective in stopping status epilepticus in some C-NORSE cases.

1. Introduction

New-onset refractory status epilepticus (NORSE) describes very long-lasting status epilepticus (SE) without a readily identifiable cause in otherwise healthy individuals. NORSE was first described by Smith in 2007 (Wilder-Smith et al., 2005). Despite extensive research efforts, around half of adult NORSE cases remain cryptogenic (Sculier and Gaspard, 2019). Although several studies have reported cryptogenic NORSE (C-NORSE) cases in which classical immunotherapies, such as high-dose corticosteroids, intravenous immunoglobulins (IVIg), or plasma exchange (PE), proved effective (Gall et al., 2013; Kodama et al., 2018), many C-NORSE cases do not respond to such therapies, and display poor outcomes (Iizuka et al., 2017).

Here we describe a case in which cessation of SE was successfully achieved using tocilizumab, an interleukin (IL)-6 receptor-blocking antibody, for C-NORSE refractory to high-dose corticosteroids, IVIg, PE, and intravenous cyclophosphamide (IVCY).

1.1. Case report

The patient was a 46-year-old woman with no significant past medical history. She was admitted to a previous hospital with new-onset generalized tonic-clonic seizures two weeks after developing headache and one week after developing fever. The patient was intubated and placed on mechanical ventilation immediately after admission. Although several oral antiepileptic drugs (AEDs), propofol, and midazolam were used, she experienced repeated convulsions of the face and right limbs for 3 days, and was transferred to our hospital.

On admission, her level of consciousness was low (Glasgow Coma Scale score 3; E1VTM1) on high-dose propofol and midazolam, and she still displayed frequent facial twitches on either side, followed by generalized convulsions. Blood tests did not reveal any metabolic disorders, and results for serum autoantibodies were negative except for anti-thyroglobulin antibody. Cerebrospinal fluid (CSF) examinations revealed elevated cell counts (40/μL). However, other general tests were normal, and results from bacterial and fungal cultures, DNA polymerase chain reaction assays for herpes simplex virus and varicella-zoster virus were negative. Autoantibodies against neuronal antigens including N-...
Fluid-attenuated inversion recovery images reveal high-intensity areas in bilateral medial temporal lobes and insulas on day 37 of admission (arrowheads). Findings from MRI of the brain.

We initiated repeated immunotherapies, including 5 courses of high-dose corticosteroids (methylprednisolone 1 g/day for 3 days), 3 courses of IVIg (0.4 g/kg/day for 5 days), 7 PE, and 2 courses of IVCY (500 mg/m²/day). However, convulsions and epileptic discharges on EEG were not controlled at all with these immunotherapies (Fig. 3).

Next, we planned to use tocilizumab, an IL-6 receptor-blocking antibody, considering that IL-6 in CSF appeared significantly high (118 pg/mL; no cut-off value has been confirmed, but a previous study suggested a cut-off of 10 pg/mL for non-herpetic acute limbic encephalitis (Ichiyama et al., 2008)) on day 137 of admission. After gaining approval from the Osaka University Clinical Research Review Committee, we administered tocilizumab on days 141 and 148 (4 mg/kg each). The frequency of convulsions gradually decreased, and we were mostly able to control convulsions using midazolam without thiamylal. We administered tocilizumab a third time (8 mg/kg) on day 187, finally achieving total control of convulsions in combination with four AEDs (perampanel at 12 mg/day, topiramate at 600 mg/day, clobazam at 15 mg/day, and lamotrigine at 300 mg/day) and no intravenous anesthetics. EEG revealed diffuse, low-amplitude slow waves, and did not show any epileptic discharges after administrations of tocilizumab on day 246 (Fig. 2C). The patient was able to be withdrawn from mechanical ventilation on day 220. IL-6 in CSF decreased markedly and was 6.4 pg/mL after the last administration of tocilizumab on day 206. Since convulsions stabilized, she was transferred to another long-term care hospital in a state of unresponsive wakefulness syndrome (modified Rankin Scale (mRS) score 5) on day 280 of admission (Fig. 3).

2. Discussion

We encountered a 46-year-old woman with C-NORSE who achieved cessation of long-lasting SE following 3 administrations of tocilizumab, although the final outcome was poor.

The etiology of NORSE is either unknown or an unusual cause only identified after extensive work-up, and can be divided in 4 categories: inflammatory and autoimmune (the most frequently identified cause; 40% of NORSE cases), uncommon infectious encephalitis, genetic disorders, and toxic disorders (Sculier and Gaspard, 2019). Around half of adult NORSE cases remain cryptogenic, despite extensive work-up (Sculier and Gaspard, 2019). C-NORSE may represent a heterogeneous group of disorders, but the clinical features are often similar to those of autoimmune cases, so some C-NORSE cases may correspond to autoimmune encephalitis associated with unidentified autoantibodies or not...
Fig. 2. EEG findings.
(A) When convulsions are controlled using high-dose thiamylal on day 9 of admission, EEG reveals a burst suppression pattern. (B) On reducing the dose of thiamylal on day 89 of admission, the patient displays frequent facial twitches on the right or left side, followed by generalized convulsions. EEG the same day reveals frequent sharp waves, mainly observed in bilateral parieto-occipital areas. An ictal EEG pattern is also observed: rhythmic $\beta$ waves start at the right central area (arrowhead), propagate to the right fronto-central area, and change to irregular spike waves. Finally, waves suddenly terminate (arrow). (C) After administrations of tocilizumab on day 246 of admission, EEG reveals diffuse, low-amplitude slow waves, and no epileptic discharges. TC = time constant; HF = high-frequency filter.

Fig. 3. Clinical course.
Intravenous anesthetics (with the exception of thiamylal), oral AEDs, and immunotherapies such as high-dose corticosteroids, IVIg, PEs, and IVCY proved totally ineffective, and the patient presented with long-lasting convulsive seizures. After 3 administrations of tocilizumab, convulsions totally resolved without intravenous anesthetics. She was able to be withdrawn from mechanical ventilation, but was in a state of unresponsive wakefulness syndrome at discharge. IL-6 concentration in CSF decreased with administrations of tocilizumab. AEDs = antiepileptic drugs; PHT = phenytoin; LEV = levetiracetam; PB = phenobarbital; CLB = clobazam; LCM = lacosamide; NaBr = sodium bromide; LTG = lamotrigine; PER = perampanel; TPM = topiramate; IVMP = intravenous methylprednisolone; PE = plasma exchange; IVIg = intravenous immunoglobulin; IVCY = intravenous cyclophosphamide; CSF = cerebrospinal fluid; IL-6 = interleukin-6; mRS = modified Rankin Scale.
associated with autoantibodies at all (Sculier and Gaspard, 2019). However, many C-NORSE cases do not respond to classical immunotherapies, such as high-dose corticosteroids, IVIg, and PE, including our case (Iizuka et al., 2017).

Previous studies have mentioned the relationship between epilepsy and IL-6 (Vezzani et al., 2011; Peltola et al., 2000). Repetitive or prolonged epileptic seizures lead to the production of proinflammatory cytokines, including IL-6, by activating microglia, astrocytes, and neurons. The inflammatory cascades activated in this manner induce disruption of the blood-brain barrier and further inflammation, thereby sustaining seizure activity (Vezzani et al., 2011). Previous studies have reported that concentrations of IL-6 in CSF and plasma were significantly increased after convulsive seizures (Peltola et al., 2000), and that anti-IL-6 treatment reduced the development of seizures in rat models of epilepsy (Leo et al., 2020). Intrathecal overproduction of IL-6 has also been described in pediatric febrile infection-related epilepsy syndrome, which corresponds to adult NORSE (Sakuma et al., 2015), suggesting that anti-IL-6 treatment might be effective against NORSE. Jun et al. reported 7 NORSE cases (6 cryptogenic cases, 1 case of anti-NMDAR encephalitis) treated with 1 or 2 doses of tocilizumab, with SE resolving immediately in 6 patients (Jun et al., 2018). Since our patient revealed negative results for already-known anti-neuronal autoantibodies and indirect immunofluorescence, and presented with elevated levels of IL-6 in CSF, the pathogenesis in this patient might not have been induced by autoantibodies, but instead by IL-6-mediated inflammatory responses. We therefore used tocilizumab in the present case. According to the immunotherapy regimens of the above case series (Jun et al., 2018), we started to administer tocilizumab at a dosage of 4 mg/kg for 2 cycles in 1-week intervals, then a third time at a dosage of 8 mg/kg almost one month later, finally achieving total control of SE. Thus, we presume anti-IL-6 treatment may prove effective for stopping SE in some C-NORSE cases, particularly those presenting with elevated levels of IL-6 in CSF.

The above case series suggest that early treatment with tocilizumab might prove more effective for better functional outcomes, since patients with good or fair outcomes (mRS score ≤ 3) in this study exhibited a relatively short duration of SE (median, 11 days) compared to other patients (median, 42 days) (Jun et al., 2018). Compared to the case series above, our case experienced a much longer duration of SE (140 days), needed more doses of tocilizumab (3 doses), and experienced a poor outcome (mRS score 5). One reason our case experienced a poor outcome may be the irreversible damage induced in the cerebral cortex by very long-lasting SE. If we had performed anti-IL-6 treatment earlier before the onset of irreversible neurological disorders, our patient might have achieved better functional outcomes. More cases and studies clearly need to be accumulated to confirm this hypothesis.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgements

The authors wish to thank Doctor Yutaro Okamoto, Doctor Mayuko Kunii, Doctor Kentaro Shimizu, and Professor Takeshi Shimazu of the Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine for systemic management of the patient. The authors also wish to thank Professor Josep Dalmau of the University of Barcelona for measuring autoantibodies against neuronal cell-surface antigens.

References

Galli, C.R., et al., 2013. Five cases of new onset refractory status epilepticus (NORSE) syndrome: outcomes with early immunotherapy. Seizure. 22, 217-220.
Ichiyama, T., et al., 2008. Cerebrospinal fluid levels of cytokines in non-herpetic acute limbic encephalitis: comparison with herpes simplex encephalitis. Cytokine. 44 (1), 149-153.
Iizuka, T., et al., 2017. Cryptogenic NORSE: its distinctive clinical features and response to immunotherapy. Neurol. Neuroimmunol. Neuroinflamm. 4 (6), e096.
Jun, J.S., et al., 2018. Tocilizumab treatment for new onset refractory status epilepticus. Ann. Neurol. 84 (6), 940–945.
Kodama, S., et al., 2018. A favorable outcome of intensive immunotherapies for new-onset refractory status epilepticus (NORSE). Intens. Care 6, 43.
Leo, A., et al., 2020. IL-6 receptor blockade by tocilizumab has anti-absence and anti-epileptogenic effects in the WAG/Rij rat model of absence epilepsy. Neurotherapeutics. 17 (4), 2004–2014.
Peltola, J., et al., 2000. Interleukin-6 and interleukin-1 receptor antagonist in cerebrospinal fluid from patients with recent tonic-clonic seizures. Epilepsy Res. 41 (3), 205–211.
Sakuma, H., et al., 2015. Intrathecal overproduction of proinflammatory cytokines and chemokines in febrile infection-related refractory status epilepticus. J. Neurol. Neurosurg. Psychiatry. 86 (7), 822-822.
Sculier, C., Gaspard, N., 2019. New onset refractory status epilepticus (NORSE). Seizure. 68, 72–78.
Vezzani, A., et al., 2011. The role of inflammation in epilepsy. Nat. Rev. Neurol. 7 (1), 31–40.
Wilder-Smith, E.P., et al., 2005. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. Ann. Acad. Med. Singap. 34 (7), 417-420.