Bridging the Gap: Tailoring an Approach to Treatment in Febrile Infection-Related Epilepsy Syndrome

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Abstract

Cytokine profiling before immunotherapy is increasingly prevalent in febrile infection-related epilepsy syndrome (FIRES). In this case, an 18-year-old man presented with first-onset seizure after a nonspecific febrile illness. He developed super-refractory status epilepticus requiring multiple antiseizure medications and general anesthetic infusions. He was treated with pulsed methylprednisolone and plasma exchange and started on ketogenic diet. Contrast-enhanced MRI brain revealed postictal changes. EEG findings showed multifocal ictal runs and generalized periodic epileptiform discharges. CSF analysis, autoantibody testing, and malignancy screening were unremarkable. Genetic testing revealed variants of uncertain significance in the CNKSR2 and OPN1LW genes. Initial serum and CSF cytokine analyses performed on days 6 and 21 revealed that interleukin (IL)–6, TNF-α, and IL-1β, are postulated to have a role in epileptogenesis in FIRES.

There is an emerging role for immunotherapy in FIRES. Pulsed steroids, plasma exchange, anakinra (IL-1Ra), and tocilizumab (anti-IL-6R) have been previously trialed.

Cytokine profiling and targeted immunotherapy in febrile infection-related epilepsy syndrome (FIRES)

How is cytokine profiling helpful in FIRES?
Serum and CSF cytokine profiling, interpreted in conjunction with an immunologist, may help guide targeted immunotherapy in FIRES.

The use of tocilizumab can be considered in patients with upregulated IL-6.

Tofacitinib was initially trialed on day 30 of admission. There was no clinical improvement, and IL-6 continued to rise. Tocilizumab was given on day 51 with significant clinical and electrographic response. Anakinra was subsequently trialed from days 99 to 103 because clinical ictal activity re-emerged on weaning anesthetics but stopped because of poor response. Serial cytokine profiles showed improvement after 7 doses of tocilizumab. There was corresponding improved seizure control. This case illustrates how personalized immunomonitoring may be helpful in cases of FIRES, where proinflammatory cytokines are postulated to act in epileptogenesis. There is an emerging role for cytokine profiling and close collaboration with immunologists for the treatment of FIRES. The use of tocilizumab may be considered in patients with FIRES with upregulated IL-6.

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Febrile infection-related epilepsy syndrome (FIRES) is a rare catastrophic epileptic encephalopathy associated with significant mortality and morbidity. The pathogenesis of FIRES remains unclear and has been postulated to involve a fulminant postinfectious inflammatory process. Previous studies have shown that certain cytokines appear to be upregulated in FIRES, and there may be an emerging role for immunotherapy in treatment of this disease. 

Cytokine profiling before immunotherapy is increasingly prevalent. However, tailoring multiple immunotherapeutic agents to the evolving immunologic profile is not commonly performed in FIRES. We describe our experience with immunologic profile-directed immunotherapy in an 18-year-old man with FIRES. Through this case, we discuss the role of cytokines in neurologic disorders, techniques used in cytokine profiling, and how this may translate to clinical practice with directed immunotherapy.

Case Report

Initial Presentation

An 18-year-old man presented with first-onset seizure a week after a nonspecific febrile illness.

He subsequently developed super-refractory status epilepticus. He received multiple lines of antiseizure medications, such as levetiracetam, valproic acid, topiramate, perampanel, phenobarbital, gabapentin, clonazepam, vigabatrin, and rufinamide and several general anesthetic infusions, including midazolam, propofol, thiopentone, and ketamine. Despite this, his EEG continued to show generalized periodic epileptiform discharges and multifocal electrographical ictal runs with associated motor manifestations of rhythmic head, eye, shoulder, and jaw movements. He was given a course of pulsed methylprednisolone and plasma exchange and started on ketogenic diet. Contrast-enhanced MRI of the brain showed diffuse brain swelling and an increased signal of the supratentorial and infratentorial gyri, consistent with postictal changes. CSF analysis did not reveal any infective etiology. Autoantibody testing and malignancy screening, which included whole body CT and ultrasound of the testes, were unremarkable.

Genetic testing revealed variants of uncertain significance (VUS) in the CNKSR2 and OPNILW genes. CNKSR2 deletion or mutation has been implicated in epilepsy-aphasia spectrum disorders. However, the mutation found in our patient has not been described to cause status epilepticus.

Cytokine Analysis

Initial serum and CSF cytokine analyses performed on days 6 and 21 (referencing the first day of admission as day 1) revealed that interleukin (IL)–6, IL-1RA, monocyte chemoattractant protein–1, macrophage inflammatory protein 1β, and interferon (IFN)–γ were highly elevated, predominantly in the CNS. This was consistent with cytokine release syndrome, whereby activated T cells or natural killer (NK) cells induce the activation of macrophages. There was worsening CSF cytokine derangement on day 21 compared with that on day 6 of admission. This correlated with C-reactive protein (CRP), ferritin, lactate dehydrogenase, alanine aminotransferase, and aspartate transaminase levels, which peaked around that period.

Tofacitinib was commenced at day 30 in view of the elevated IFN-γ suggesting increased T and NK cell activity and its superior CNS penetration compared with monoclonal antibodies. After 3 weeks of therapy, electrographic improvement was inconsistent. IL-6 levels continued to rise (eTable 1, links.lww.com/WNL/C652); hence, 8 mg/kg of tocilizumab was added on day 51. Improvement in CRP was observed after day 65, and significant electrographic improvement was noted at day 67 (Figure). The previous bihemispheric independent epileptiform abnormalities, which frequently evolved into electrographical ictal runs, had become less frequent periodic discharges, with greater lengths of suppression seen. This facilitated the reduction of midazolam and ketamine infusions. Tocilizumab was dosed at 2-weekly intervals for the first 4 doses. Daily subcutaneous anakinra was also given after 4 doses of tocilizumab (from day 99 to day 103) because of the re-emergence of organized periodic discharges with concomitant motor manifestations on weaning anesthetic infusions. This was stopped after 5 days because of the lack of clinical and electrographic responses. Monthly tocilizumab was instituted as maintenance therapy, and tofacitinib was stopped on day 103. Plasma IL-6 levels had decreased markedly when checked on day 163.

Serial Cytokine Analysis

Serial cytokine profiling showed improvement and subsequent near-normalization of cytokine levels after 7 doses of tocilizumab were given over 5 months (eTable 1, links.lww.com/WNL/C652). CRP (peak 267 mg/L, normal range 0–10 mg/L) and ferritin levels (peak 1,322 μg/L, normal range: 20–300 μg/L) had also normalized with treatment. This was commensurate with improved seizure control. He was weaned off anesthetic infusions completely at day 125 of admission. Currently, at day 249, the patient is in a minimally conscious state and undergoing rehabilitation. His current antiseizure medication regime, consisting of levetiracetam, phenobarbital, perampanel, rufinamide, vigabatrin, and clozazepam, is being gradually down-titrated. The interval of tocilizumab dosing has also been lengthened, given the sustained improvement in his cytokine profile.

Discussion

There is an increasing recognition of the role cytokines play in various disease processes.

What Are Cytokines?

Cytokines are small molecules involved in intercellular communication and are classified into categories such as interleukins, interferons, and tumor necrosis factors. A complex
interplay between cytokines mediates the immune response. Cytokine release syndrome (CRS), or “cytokine storm,” occurs where a dysregulated immune response is triggered inappropriately. In CRS, proinflammatory cytokines and excessive immune cell hyperactivation cause severe systemic inflammatory syndrome and multiorgan dysfunction. C-reactive protein and ferritin are usually elevated, and patients may have cytopenias. IFN-γ, IL-1, IL-6, tumor necrosis factor (TNF), and IL-18 are often elevated in CRS and believed to have central immunopathologic roles. More recently, CRS was recognized to play a role in severe coronavirus disease 2019 (COVID-19) infection and immune-related adverse events (irAEs) from immune checkpoint inhibitors. For example, elevated serum IL-6 levels have been found in both patients with severe COVID-19 infection and irAEs, for which tocilizumab, an anti-IL-6 receptor monoclonal antibody, was demonstrated to be efficacious.5,6

What Is Cytokine Profiling?
Cytokine profiling can be performed with various technologies, including ELISA, cytometric bead array, LumineX, and Meso Scale Discovery. Caution ought to be exercised in the comparisons of results across different methods of profiling because large interlaboratory variations exist. Furthermore, each technology has differing test sensitivities and accurate detection ranges.7

Cytokine profiling in various disease states can provide valuable insights into disease pathogenesis and potential therapeutic targets. In patients with neuromyelitis optica spectrum disorder (NMOSD), IL-6 was found to be significantly elevated in both the serum and CSF and correlated with disability.8 It is postulated that IL-6 plays an important role in NMOSD pathogenesis by promoting plasmablast survival, disrupting the blood-brain barrier and stimulating antibody production against aquaporin-4.8 This provides the basis for the use of novel therapies in NMOSD, such as the anti–IL-6 receptor monoclonal antibody satralizumab.

Beyond classically neuroinflammatory diseases, there is an increasing evidence for the role of cytokines in the pathogenesis of epilepsy. It has been shown that seizures can lead to...
cytokine production. This promotes further inflammatory changes such as the potentiation of free radical species, alterations in glutamatergic neurotransmission, and disruption of the blood-brain barrier, which results in the development and progression of epilepsy. Experimental animal models have shown postictal IL-1β expression in microglia and astrocytes and demonstrated that IL-1β enhances neuronal excitability. A meta-analysis of patients with epilepsy has also demonstrated elevated levels of serum IL-6, IL-17 and CSF IL-1β, IL-10 in these patients. Clinical Use of Cytokine Profiling in FIRES

In FIRES, proinflammatory cytokines such as IL-6, TNF-α, and IL-1β are postulated to act in neuroexcitability and epileptogenesis. In a comparison of CSF cytokine profiles in pediatric patients with epilepsy, patients with FIRES were found to have a higher elevation of cytokines compared with patients with febrile status epilepticus and chronic epilepsy, particularly in Th-1–associated cytokines such as IL-6 and TNF-α. When cytokine profiles were compared between pediatric patients with FIRES and those with other inflammatory neurologic diseases, patients with FIRES were noted to have significantly increased IL-6, IL-8, and CXCL10 levels. These changes were more marked in the CSF than in the serum. Jun et al. also described a group of adult patients with new-onset refractory status epilepticus in whom cytokine analysis was performed, showing highly upregulated CSF IL-6. Most patients of this group responded to tocilizumab treatment. Studies in animal models and small numbers of patients indicate that IL-1R signaling is also implicated in initiating the neuroinflammatory cascade. In the study conducted by Clarkson et al. on patients with FIRES, levels of CSF IL-1RA were found to be elevated (similar to our patient). However, these patients demonstrated attenuated inhibition of IL-1R signaling, which suggests a functional deficit in IL-1RA. This provides the pathophysiologic basis for the treatment of FIRES with targeted immunotherapy.

In our patient, the immunologic profile was noted to be markedly variable across different time points, and the therapeutic regimen was modified accordingly. Unfortunately, given the overlap of treatment periods with tofacitinib and tocilizumab in this case, it is unclear whether the changes in cytokine levels are attributable to 1 drug or both in tandem. Tailoring of multimodal immunotherapy based on serial cytokine profiling is infrequently performed and mostly restricted to treatment failure in FIRES in case reports. Furthermore, in most cases of FIRES, CSF and serum cytokine profiling seem concordant, although there have been reports of CNS-restricted IL-6 elevation. In our patient, the cytokine derangement within the first few weeks of presentation was observed predominantly in the CNS, rather than the serum. This suggests that CSF cytokine analysis should be considered in FIRES to avoid missing cases of CNS-restricted inflammation. The interplay between inflammation and ictogenesis is complex, and additional mechanistic analyses of FIRES pathogenesis are required. Personalized immunomonitoring before and during treatment, with appropriately targeted therapy, may be helpful in FIRES.

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