New-Onset Refractory Status Epilepticus

Recognizing NORSE as a clinical presentation is meant to lead to improved research and communication that hopefully may improve outcomes eventually.

By Michelle L. Dougherty, MD, FAAN, FAES

History and Definitions

Status epilepticus (SE) is a common neurologic emergency. In most cases, a clear etiology, such as missed doses of medications, can be found quickly with routine evaluation. In rare cases, however, SE persists, and no etiology can be ascertained; this condition is now termed new-onset refractory status epilepticus (NORSE). When NORSE occurs, the treating neurologist is faced with the daunting task of trying to prevent ongoing neurologic injury caused by SE without the key component crucial to stopping SE—treatment directed toward the inciting etiology. Previously, the etiology for people with NORSE was often presumed to be viral encephalitis; however, there are at least 181 identified uncommon etiologies of SE.[1,2] These causes of SE include immunologic disorders, mitochondrial disorders, infectious diseases, genetic disorders, drugs, toxins, and other causes.[1]

First characterized in 2005 as a clinical syndrome, the term *NORSE* was used to describe a cohort of 7 female patients, age 20 to 52 years and previously in good health, who fell ill with fever (5 of 7), had refractory SE, and underwent extensive medical evaluation and testing with no clear etiology determined. [3] This catastrophic syndrome has also been recognized and described in the literature by alternate names including idiopathic catastrophic epileptic encephalopathy, febrile illness-related epilepsy syndrome (FIRES), acute encephalitis with refractory repetitive partial seizures (AERRPS), devastating epilepsy in school-aged children (DESC), acute encephalopathy with inflammation-mediated SE (AEIMSE), severe refractory SE owing to presumed encephalitis, and de novo cryptogenic refractory multifocal febrile SE.[2,4,5] Patients described in these reports were reported to be previously healthy individuals who developed a super-refractory SE, usually preceded by a febrile illness and commonly associated with findings of inflammatory markers in cerebrospinal fluid (CSF) and unknown etiology after extensive evaluation.

Because of varying terminology in use, a group of experts recently met to clarify terminology with a goal of promoting research, communication, early diagnosis, and prompt appropriate medical care.[2] They reported the consensus definition of NORSE as "a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurologic disorder, with new onset of refractory SE without a clear acute or active structural, toxic, or metabolic cause." This definition includes patients with viral or autoimmune causes. If no cause is found after extensive evaluation, this is considered *cryptogenic NORSE* or *NORSE of unknown etiology*.[2,6] As further clarification, FIRES is now considered "a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours before onset of refractory SE, with or without fever at onset of SE."[2]

Pathophysiology

Because there may be many etiologies involved, little can be said about the pathophysiology definitively. Many reports have suggested an inflammatory component involving intrathecal overproduction of cytokines with proconvulsant activity, and increased levels of interleukin 6, C-X-C motif chemokine 10, and interleukin 8 in CSF have been reported.[4] It is currently unclear, however, if inflammation represents a cause of the SE in NORSE or is the effect of ongoing SE.[2]

Diagnostic Evaluation

A 2015 review found that 52% of cases of NORSE (n = 130) remained cryptogenic despite extensive evaluation. When etiologies were found, the most common were autoimmune or paraneoplastic in origin.[7] The recommended evaluation for NORSE is extensive and still in evolution. Currently, a far-reaching evaluation is recommended and includes consideration of infectious, autoimmune, paraneoplastic, neoplastic, metabolic, toxic, and genetic etiologies.

Where indicated, additional testing may be necessary for patients at risk for environmental exposures (eg, zoonotic, vectorborne, geographic, or seasonal exposures). The interested reader is directed to the NORSE Institute at www.norseinstitute.org for the most up-to-date comprehensive recommendations.

A comprehensive evaluation should also include continuous EEG (cEEG), MRI, and lumbar puncture for CSF analysis. Many centers have cEEG readily available for diagnosis. Several EEG findings have been reported in cases of NORSE.[2,7] Early in the course of illness, there can be a pattern of brief infrequent seizures evolving to SE. The reported characteristic EEG seizure pattern consists of prolonged focal fast followed by a gradual well-formed spike-wave complexes. Beta-delta complexes, resembling extreme delta brush, have also been reported. Multiple seizure types on EEG and periodic discharges have been described that include—in decreasing order of frequency—unilateral, bilaterally independent, generalized, and multifocal.[7] Reported in approximately 62% of cases, MRI abnormalities are common and predominantly involve limbic and/or neocortical structures.[7] Abnormal CSF findings of pleocytosis and/or elevated protein were found in 73% of cases.[7]

Treatment

If a specific etiology is found, treatment should be directed at that etiology. In the absence of an etiology or while evaluation is underway, there is unfortunately little definitive information regarding treatment. Guidance that is available comes from small case series. There is no generally accepted treatment for NORSE, and there is limited success with antiepileptic drugs (AEDs).[2] Some of the available data from case series support use of early immunotherapy in the absence of a definite etiology including high dose steroids, intravenous immunoglobulins (IVIG), and plasmapheresis (PLEX).[6,7]

In a series of 11 persons with continuous NORSE, 10 patients were treated with first-line immunotherapy (ie, methylprednisolone, PLEX, and IVIG), but treatment was considered effective for only 2 of them.[4] Of 5 patients in this series treated with IV cyclophosphamide, treatment was considered effective for 4 of them.

In a different case series of 5 patients with NORSE, 3 had a good response to early immunotherapy.[5]

Another case series of 7 patients who had immunotherapy (including rituximab for 5 of the 7) that failed to terminate SE were subsequently treated with tocilizumab, an interleukin-6 receptor inhibitor. Seizure cessation was observed in 6 of 7 of these patients within 2 to 10 days of tocilizumab administration.[8] Other treatments potentially worthy of further study due to anti-inflammatory mechanisms or data supportive of efficacy in refractory SE include the ketogenic diet, cannabidiol, anakinra, and therapeutic hypothermia.[2]

Prognosis

The prognosis for individuals with NORSE is generally poor; NORSE is often fatal or leaves the affected patient with severe residual encephalopathy and epilepsy. In available follow-up data, poor outcome at discharge, defined as a Modified Rankin Scale (mRS) score of 4 to 5, was seen in 49 of 125 patients who had NORSE; furthermore, 28 of the 125 patients died. Medical complications and duration of SE have been identified as predictors of poor outcome. However, in longer-term follow-up, some improvement was noted after discharge with the majority of patients who were not lost to follow-up having improvements in their mRS scores to 0 to 3 at their last visit.[7]

Summary

Newly recognized, NORSE is a clinical presentation of a rare but often devastating neurologic emergency. Establishing a consensus definition is a preliminary step that hopefully will lead to a more coordinated and fruitful research effort to identify and treat the possibly multiple etiologies of NORSE. Although many cases of NORSE remain cryptogenic, a cause was ultimately identified in 48% of cases with a paraneoplastic or autoimmune etiology as most common.[7] Research is ongoing and a registry administered through the NORSE Institute has an initial aim to enroll 100 patients with NORSE over 2 years to collect and review clinical data including critical-care course; findings from EEG, MRI, CSF, and serum analysis; brain tissue samples; and clinical outcomes.[2] There is a signal that a careful and thorough evaluation can lead to better diagnosis, treatment, and outcomes. ■

1. Tan RYL, Neligan A, Shorvon SD. The uncommon causes of status epilepticus: a systematic review. *Epilepsy Res*. 2010;91(2-3):111-122.
2. Gaspard N, Hirsch LJ, Sculier C, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. *Epilepsia*. 2018;59:745-752.
3. Wilder-Smith EPV, Lim EC, Teoh HL, et al. The NORSE (new-onset refractory status epilepticus) syndrome: defining a disease entity. *Ann Acad Med Singapore*. 2005;34:417-420.
4. Iizuka T, Kanazawa N, Kaneko J, et al. Cryptogenic NORSE: its distinctive clinical features and response to immunotherapy. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e396.
5. Gall CRE, Jumma O, Mohanraj R. Five cases of new onset refractory status epilepticus (NORSE) syndrome: outcomes with early immunotherapy. *Seizure*. 2013;22:217-220.
6. Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. *Epilepsia*. 2018;59:739-744.
7. Gaspard N, Foreman BP, Alvarez V, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology*. 2015;85:1604-1613.
8. Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. *Ann Neurol*. 2018;84:940-954.

Michelle L. Dougherty, MD, FAAN, FAES
Chief Medical Officer
Neurotech, LLC
Waukesha, WI
Assistant Professor of Neurology
Drexel Neurosciences Institute
Philadelphia, PA