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Understanding new-onset refractory status epilepticus from an immunological point of view

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New-onset refractory status epilepticus (NORSE) is unexpected onset of refractory status epilepticus in individuals with no preexisting relevant neurologic condition. The etiologies remain largely cryptogenic; treatment is challenging after failure to control seizures despite use of multiple antiepileptic drugs and anesthetic agents. Frequent fever and other infectious prodromes, elevated proinflammatory cytokine/chemokine levels, and limbic or multifocal brain lesions indicate active inflammation in NORSE. Among identified causes, autoimmune encephalitis is the most common and accounts for more than one-third of all known NORSE cases, followed by infection-related etiologies. Although more evidence is needed, anti-cytokine therapies with tocilizumab and anakinra along with other immunotherapeutic agents used in autoimmune encephalitis can aid in alleviating or hindering the inflammatory cascade and controlling seizures.

Keywords: New-onset refractory status epilepticus, Etiology, Autoimmune, Inflammation, Cryptogenic

Introduction

Status epilepticus (SE) is an emergent and severe neurologic condition involving persistent or recurrent seizures. Approximately 30% to 40% of patients with SE are refractory (RSE) to first- and second-line treatments, which results in high mobility and mortality [1-3]. New-onset RSE (NORSE) refers to a specific clinical presentation where RSE occurs in patients without active epilepsy or other preexisting relevant neurologic disorders and without clear acute or active structural, toxic, or metabolic causes [4,5]. Management of NORSE is challenging because its underlying etiology is not identifiable readily, and antiepileptic drugs and anesthetic agents often fail to control seizures [4,6,7]. Although the etiologies of NORSE remain cryptogenic in most cases, autoimmune and infectious factors are present in at least 30% to 40% of cases, and fever or other infectious prodrome is frequent, suggesting an immune-mediated pathogenesis [4,6-8]. This review introduces neuroinflammatory perspectives of NORSE from etiology to therapeutic strategies.

Neuroinflammatory etiology in new-onset refractory status epilepticus

Several studies have reported that more than half of RSE cases have an acute symptomatic etiology, especially encephalitis or inflammatory etiologies [2,3,9]. NORSE excludes structural, toxic, and metabolic causes by consensus definition [5]; in addition, acute symptomatic etiologies (including infection and inflammation) account for a larger proportion of NORSE than of RSE cases in general.

In several studies, non-paraneoplastic and paraneoplastic autoimmune encephalitis have been the most frequently identified causes of NORSE [4,7,8,10]. Autoantibodies to the *N*-methyl-D-aspartate (NMDA) receptor are the most common among identified autoantibodies in autoimmune encephalitis and frequently are identified as a cause of NORSE along with encephalitis associated with antibodies to the voltage-gated potassium channel complex, which are distinguished into anti-leucine-rich

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glioma-inactivated 1 (LGI1) and anti-contactin associated protein 2 (CASPR2) [4].

In more than half of NORSE cases, the etiology is unclear, and these cases are categorized as cryptogenic [4,7]. One reason for the large proportion of cryptogenic cases could be a less extensive work-up. Recently, the etiology in three of 26 NORSE patients was discovered only after brain biopsy and/or autopsy [7]. Autoimmune encephalitis associated with unidentified antibodies could be another cause of cryptogenic NORSE. However, a study by Iizuka et al. [6] that compared cryptogenic NORSE with anti-NMDA receptor encephalitis showed distinguishing clinical and immunological features. In that study, patients with cryptogenic NORSE demonstrated less cerebrospinal fluid (CSF) pleocytosis, no oligoclonal bands in the CSF, and a rarely elevated immunoglobulin G (IgG) index. Immunohistochemistry using a rat brain or hippocampal culture also did not show evidence of antineuronal antigens. Clinically, there were no psychobehavioral or memory alterations and infrequent involuntary movements. However, that study also found that most patients with cryptogenic NORSE had prodromal fever and brain magnetic resonance imaging (MRI) abnormalities, and median protein levels in the CSF were higher than those typically seen in anti-NMDA receptor encephalitis, indicating an underlying inflammation-mediated mechanism.

Febrile infection-related epilepsy syndrome (FIRES) is a subcategory of NORSE that presents with a prior febrile infection occurring between 2 weeks and 24 hours prior to onset of RSE [5]. FIRES often is discussed separately from NORSE because of its distinct age distribution (mostly in children) and clear history of febrile illness. However, the clinical manifestations, disease course, and outcomes are similar in FIRES and other types of NORSE, and these two conditions are considered to have a largely shared pathophysiology. A report of an association between FIRES and an *IL1RN* gene polymorphism supports an inflammation-mediated pathogenesis [11]. That study also suggests that more investigation is needed into genetic factors that affect the immune response in such patients.

SE is associated with several preinflammatory pathways, such as the nuclear factor-κB (NF-κB) signaling pathway, the mechanistic target of rapamycin (mTOR) signaling pathway, the mitogen-activated protein kinase (MAPK) signaling pathway, and the transforming growth factor-β (TGF-β) signaling pathway [12]. Previous studies that have examined the serum and CSF in NORSE and FIRES patients have reported upregulation of multiple cytokines/chemokines [13-15]. TGF-β signaling pathways also are involved in blood-brain barrier (BBB) disruption, which contributes to SE and epileptogenesis [16]. More than half of NORSE patients showed MRI abnormalities at the initial or follow-up evaluation and also frequently demonstrated limbic area involvement [4,6-8,17]. Leptomeningeal enhancement indicating BBB disruption has been reported in NORSE patients at variable proportions and is associated with both pharmacoresistance and poor functional outcome [4,8,17].

Therefore, autoimmune and other neuroinflammatory etiologies mainly are involved in NORSE pathogenesis, and the initial noninflammatory neurological condition can accompany neuroinflammation under SE and involve epileptogenesis due to BBB disruption and excitotoxic neuronal damage, which all lead to a fulminant inflammatory response in the brain.

Etiologic evaluation of NORSE

Initial patient evaluation includes brain MRI, electroencephalogram, CSF study, and blood analysis. Brain MRI can identify structural lesions or show evidence of neuroinflammation. CSF pleocytosis and elevated CSF protein levels can aid in identifying neuroinflammation during its initial stages. Autoimmune and infectious causes must be evaluated thoroughly considering the large number of identifiable etiologies. A list of suggested screening investigations in NORSE patients is summarized in Table 1. A cytokine assay of serum and CSF can provide supportive evidence of neuroinflammation and aid in therapeutic decision-making. If cancer is suspected, a computed tomography scan of the chest, abdomen, and pelvis or whole-body positron emission tomography should be conducted. Pelvic MRI is a feasible alternative for diagnosing ovarian teratoma if anti-NMDA receptor encephalitis is suspected. Metabolic and toxicological screening and genetic investigation also can help identify noninflammatory causes of NORSE. If there is an identifiable brain lesion of unknown etiology on MRI, brain biopsy can be indicated.

Immunologic treatment in NORSE

NORSE occurs in individuals without a previous history of epilepsy or other neurologic conditions and often presents with a prodromal phase followed by a progressive build-up of seizures. Initial MRIs often show no abnormality, but subsequent limbic or extra-limbic lesion development has been reported. Considering its clinical course, NORSE is classified as a rapid progressive encephalitic condition accompanied by uncontrolled seizures. Resistance to antiepileptic drugs is an important characteristic of epilepsy with an autoimmune etiology [18], and active

Table 1 A list of suggested screening investigations in NORSE

Autoimmune	Antineuronal surface autoantibodies: NMDAR, LGI1, CASPR2, $GABA_AR$, $GABA_BR$, AMPAR, glycine receptor
	Paraneoplastic/intracellular antigens: Hu, Yo, Ri, CRMP5, Ma2, GAD65, and amphiphysin
	Other serologies: ANA, ANCA, anti-thyroid antibodies
	Oligoclonal band
	Might extend to other known autoantibodies associated with CNS disorders
Infectious	CSF PCR for HSV1/2, VZV, EBV, HIV
	Bacterial and fungal stains and cultures
	Work-up for mycobacterial tuberculosis
	VDRL
	Might extend to other neuroinfectious agents. A more extensive list should be considered for immunocompromised patients including *Cryptococcus* species, *Toxoplasma gondii*, *Histoplasma capsulatum*, JC virus, CMV, HHV6, parvovirus, and WNV (endemic areas)
	Also consider metagenomic study to identify possible infectious etiologies

NORSE, new-onset refractory status epilepticus; NMDAR, *N*-methyl-D-aspartate receptor; LGI1, leucine-rich glioma-inactivated 1; CASPR2, contactin associated protein 2; $GABA_AR$, gamma-aminobutyric acid A receptor; $GABA_BR$, GABA B receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CRMP5, collapsin response mediator protein 5; GAD65, glutamic acid decarboxylase; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CNS, central nervous system; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HSV, herpes simplex virus; VZV, varicella-zoster virus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; VDRL, venereal disease research laboratory; CMV, cytomegalovirus; HHV6, human herpesvirus 6; WNV, West-Nile virus.

inflammation is observed in drug-resistant epilepsy and RSE of diverse causes [19]. Therefore, early initiation of immunotherapy can aid in alleviating or hindering the inflammatory cascade in the brain and reducing irreversible damage. However, evidence is lacking on whether timely intervention for neuroinflammation can alter the disease course and outcomes in NORSE.

Typical initial treatments include broad immune suppression and BBB stabilization with a steroid and neutralizing and competing potential autoantibodies along with normalized immune milieu using intravenous Ig and/or plasma exchanges. Rituximab, which targets CD20-expressing B cells, and lymphocyte-targeting antiproliferative agents (such as cyclophosphamide, mycophenolate mofetil, and azathioprine) are among the available choices in cases with persistent seizures. These strategies are based on immunotherapies that have been successfully administered to autoimmune encephalitis patients [20].

Tocilizumab is a monoclonal antibody that targets the interleukin (IL)-6 receptor. An investigation into the increase in proinflammatory cytokines in adult patients with NORSE showed substantial upregulation of IL-6 along with significant increase in IL-2, IL-4, IL-5, IL-10, and tumor necrosis factor-α (TNFα) in the CSF [13]. In this prior study, tocilizumab successfully controlled SE in six of seven patients. A study of acute encephalitis patients with refractory repetitive partial seizures revealed upregulation of IL-6, C-X-C motif chemokine (CXCL) 10, and IL-8 in the CSF [14]. Another study that investigated FIRES also showed increase in T helper cell type 1-associated cytokines/chemokines (TNFα, CXCL9, CXCL10, and CXCL11), IL-6, C-C motif ligand (CCL) 2, CCL19, and CXCL1 [15]. IL-6 is one of the most important proinflammatory mediators in neuroinflammation; previous studies consistently have reported upregulation of IL-6 in NORSE/FIRES patients, supporting the use of tocilizumab. However, further studies evaluating the therapeutic benefit of tocilizumab in NORSE are needed.

Anakinra is an IL-1 receptor antagonist that inhibits the biological actions of IL-1β and is used in a variety of autoinflammatory disorders [21]. Along with IL-6, IL-1β is implicated in neuronal hyperexcitability and seizures. After the first case report of the effectiveness of anakinra in FIRES [22], subsequent publications have supported the therapeutic effect of anakinra in FIRES patients [23-25]. However, another study found that administration of anakinra did not control seizures in a FIRES patient before additional treatment with tocilizumab [26]. In addition, increase of IL-1β has not been consistent in previous reports [15,22,23], although downstream proinflammatory cytokines/chemokines induced by IL-1β often are elevated in these patients. There is a lack of reporting of anakinra treatment in NORSE patients without FIRES.

Tofacitinib is a Janus kinase (JAK) inhibitor and can be used in several autoimmune and inflammatory disorders, including rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis [27]. Tofacitinib has been reported to penetrate the BBB and exert a potentially therapeutic effect in neuroinflammatory conditions [28,29]. Recently, tofacitinib was administered to NORSE patients in a study in which two of the eight NORSE patients showed a good response [30]. Further studies are needed to replicate these results and determine whether administration of this drug could increase the efficacy of treatment.

Table 2 A summary of the literature on prognosis of NORSE

Study	No. of patients	Female, n (%)	Age (yr)	Treatment duration	Follow-up	Outcome
Gaspard et al. [4]	130	62 (48)	Bimodal distribution with peaks at 28.5 and 65.5 (range, 18–81)	Hospital days: median, 32 (IQR, 17–57) days ICU stay: median, 15 (IQR, 5–36) days Duration of SE: median, 5 (2–16) days	Median, 9 (IQR, 4–19) months	At discharge - Good or fair (mRS, 0–3): 48/125 (38%) - Deaths: 28/125 (22%) Follow-up - Good or fair (mRS, 0–3): 50/63 (79%) - Deaths: 3/63 (5%) - Seizure or on AEDs: 58/63 (92%)
Khawaja et al. [10]	11	9 (82)	Median, 48 (range, 21–90)	Duration of SE: median, 54.4 (range, 12–110) days	Not reported	At discharge - Favorable outcome[a]: 6/11 (55%) - Deaths: 3/11 (27%)
Iizuka et al. [6]	11[b]	7 (64)	Median, 27 (range, 17–59)	Hospital days: median, 173 days (range, 52 days –11 months) Ventilator support: median, 38 days (range, 13 days–6 months)	Median, 11 (range, 6–111) months	At discharge - Good (mRS, 0–2): 2/11 (18%) - Deaths: 0/11 (0%) Follow-up - Good (mRS, 0–2): 3/11 (27%) - Deaths: 1/11 (9%)
Meletti et al. [38]	12[c]	7 (58)	Median, 27 (range, 17–38)	Not reported	Not reported	Normal life: 3/12 (25%) Deaths: 2/12 (17%) Seizures or on AEDs: 9/10 (90%)
Choi et al. [39]	13	6 (46)	Median, 45 (IQR, 33–49)	Hospital days: median, 46 (32.5–91) days median, 46 (IQR, 32.5–91) days ICU stay: median, 21 (IQR, 15.5–69) days	Not reported	Good (mRS, 0–2): 6/13 (46%) Deaths: 3/13 (23%)
Strohm et al. [40]	12	10 (83)	Median, 33 (range, 14–63)	Hospital days: median, 48.5 (range, 19–199) days Duration of SE: median, 12 (range, 3–106) days	Median, 509 (range, 63–1,827) days	At discharge - mRS: median, 4 (range, 2–5) Follow-up - Good (mRS, 0–2): 6/9 (67%) - Deaths: 1/9 (11%) - Clinical seizures at follow-up: 5/9 (56%)
Gugger et al. [8]	20	10 (50)	Median, 50.5 (IQR, 29–69.5)	Hospital days: median, 47.5 (IQR, 25–69) days ICU stay: median, 29.5 (IQR, 16.5–43.5) days Duration of SE: median, 10 (IQR, 7–25) days Ventilator support: median, 16 (IQR, 12.5–28) days	Median, 14 (IQR, 2–42) months	Good outcome (mRS: 0–2): 8/20 (40%) Deaths: 7/20 (35%) Diagnosis of epilepsy at the last follow-up: 12/15 (80%)
Matthews et al. [7]	26	18 (69)	Bimodal distribution with peaks at 27 and 63	Hospital days: median, 40 (IQR, 27–72) days ICU stay: median, 32 (IQR, 21–49) days Duration of SE: median, 17 (IQR, 11–46) days	Median, 9 (IQR, 2–22) months	At discharge - Good or fair (mRS, 0–3): 6/23 (23%) - Deaths: 6/23 (23%) Follow-up - Good or fair (mRS, 0–3): 12/17 (71%) - Need for long-term AEDs: 15/17 (88%)

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Table 2 Continued

Study	No. of patients	Female, n (%)	Age (yr)	Treatment duration	Follow-up	Outcome
Kim et al. [17]	39	15 (38)	Median, 33 (IQR, 22–42)	Duration of SE: median, 22 (IQR, 14–42) days	Median, 147 (IQR, 80–237) days	At discharge - Good (GOS ≥ 4): 21/39 - Deaths: 4/39 (10%) Follow-up - Seizures or on AEDs: 30/39 (77%)

NORSE, new-onset refractory status epilepticus; IQR, interquartile range; ICU, intensive care unit; SE, status epilepticus; mRS, modified Rankin scale; AED, antiepileptic drug; GOS, Glasgow outcome scale.
[a]Any outcome other than death, vegetative state, or inability to take care of oneself. [b]All patients were diagnosed with cryptogenic NORSE. [c]All patients had a claustrum sign (a hyperintense claustral signal on T2-weighted images). Only personal cases from the authors' caseloads were included.

A ketogenic diet is thought to have both anti-inflammatory and neuroprotective effects along with anti-seizure effects [19]. Many reports have shown that a ketogenic diet can aid in seizure control and improve cognitive outcomes in FIRES [31-33]. Investigations into use of a ketogenic diet in NORSE patients have suggested a potential therapeutic benefit [8,34].

Vagus nerve stimulation (VNS) also can modulate the immune response via a cholinergic anti-inflammatory pathway [35]. A case report demonstrated a reduction in seizure activity with VNS in NORSE as well as other RSE patients [36,37].

Outcomes in NORSE patients

The outcomes in NORSE patients can vary by etiology and treatment, but full recovery is infrequent. Many survivors suffer from long-term cognitive and behavioral sequelae in addition to epilepsy. The reported mortality is substantial, ranging from 5% to 35%. Among survivors, 56% to 92% continue to experience seizures or need to be maintained on antiepileptic drugs [4,6-8,10,17,38-40]. All prior reports with more than 10 cases of adult NORSE patients are summarized in Table 2.

Conclusion

NORSE is a devastating condition that is refractory to antiepileptic and anesthetic medications. Poor understanding of the pathophysiologic mechanism combined with unknown and potentially diverse, rare etiologies often complicate identification of treatments optimized by patient, resulting in substantial morbidity and high mortality. However, recent progress in the understanding of autoimmune encephalitis has aided in additional identification of etiologies in NORSE patients and has led to new treatment options, including immunomodulatory therapies. Active investigation into the etiology of NORSE will help further establish a treatment plan. Brain biopsy and genetic investigations could help provide clues to the pathogenesis of this condition in some cases. Further investigation is needed to extend our understanding of the causes of NORSE and to accumulate more evidence for evaluating the efficacies of different immunomodulatory therapies.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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