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A retrospective cohort study of new-onset refractory status epilepticus (NORSE): clinical features, timing of immunotherapy and outcomes

Katherine Werbaneth[1], Melissa Mausolf[1], Jordan Seliger[2], Scheherazade Le[1]

[1] Stanford Comprehensive Epilepsy Center, Department of Neurology, 213 Quarry Road, 5979, Palo Alto 94304, California USA
[2] Stanford Neuroscience Clinical Research Group

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ABSTRACT

Objective. To describe clinical characteristics associated with immunotherapy in patients with new-onset refractory status epilepticus (NORSE) and assess its timing and effect on outcomes at hospital discharge after six and 12 months of follow-up. Our secondary aim was to apply the cryptogenic NORSE (C-NORSE) score to subjects in order to evaluate its utility in identifying C-NORSE in our cohort.

Methods. This was a retrospective single university hospital cohort study (2004-2021) of adults and children with NORSE. First-line immunotherapy was defined as corticosteroids, intravenous immunoglobulin (IVIg), and plasmapheresis (PLEX). Early immunotherapy was defined as administration of a first-line agent within seven days of presentation.

Results. Twenty-one subjects with NORSE were identified between 2004 and 2021, which was cryptogenic in 18 and immune-mediated in three. All patients received immunotherapy. Seventeen patients received early immunotherapy (81%). There was no significant difference between early versus late immunotherapy regarding "good or favorable" outcomes (mRS 0-2) at hospital discharge or during follow-up. For cryptogenic NORSE patients, 7/11 (64%) achieved good outcomes at six months, 9/11 (82%) at 12 months, and 8/10 (80%) at the last follow-up visit at >13 months. For immune-mediated NORSE patients, 3/3 (100%) achieved good outcomes at six months and 2/2 (100%) at the last follow-up visit at >13 months. In our cohort, a C-NORSE score of $\geq$5 was obtained in 12/18 (67%) of cryptogenic cases and a score <5 in all three immune-mediated cases.

Significance. There is a paucity of published data on the timing of immunotherapy for NORSE. Although at our institution early administration of immunotherapy is feasible, more research is needed to determine which patients may benefit from immunotherapy and if the timing of immunotherapy affects short and long-term outcomes. Among the patients who survived hospitalization, long-term follow-up of our NORSE cohort demonstrated that a subset achieved good mRS (0-2) scores.

Key words: NORSE, immunotherapy, C-NORSE

• **Correspondence:**
Scheherazade Le
Stanford Comprehensive Epilepsy Center,
Department of Neurology,
213 Quarry Road, 5979,
Palo Alto 94304,
California USA
<schele@stanford.edu>

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New-onset refractory status epilepticus (NORSE) is a clinical presentation in a patient without active epilepsy or a pre-existing relevant neurological disorder and without a clear, acute or active structural, toxic or metabolic cause [1]. With prolonged, refractory seizures, the outcome is generally poor in 62% of patients and the mortality rate of NORSE is up to 22-30% [2]. Extensive diagnostic evaluations are performed to uncover the etiologies of NORSE, but the causes are identified in only about half of the cases [2]. A subset of patients with NORSE have autoimmune (19%) or paraneoplastic (18%) causes which are potentially treatable. However, the diagnostic work-up and treatment of NORSE are not standardized and there are no published guidelines regarding the treatment options, such as type or timing of immunotherapy [2, 3]. Although there have been attempts at establishing an approach to NORSE [4, 5], according to an electronic survey about 25% of providers would never perform an autoimmune work-up and many would never use intravenous immunoglobulins (IVIg), plasmapheresis (PLEX), nor steroid-sparing immunosuppressants [3]. Based on Class IV evidence, conventional immunotherapies such as steroids, IVIg and PLEX are used as treatment for NORSE with often unclear or disappointing results, with no studies comparing the efficacy of the types of immunotherapy [1, 5-7]. Reports on case series have suggested that patients may benefit from early immunotherapy though the definition of "early" has not been well established [8-11]. However, if a subset of cases with an immune-mediated NORSE can be identified and treated early on, could there be improved patient outcomes?

The C-NORSE score was devised by Iizuka and colleagues in 2017 and is the sum of six clinical features and initial conventional diagnostic tests intended to differentiate C-NORSE from antibody (Ab)-mediated encephalitis at an early stage [12]. The etiology of NORSE has been reported to be more likely cryptogenic when a patient achieves a C-NORSE score of $\geq$5 out of 6 total points. A patient can be diagnosed with C-NORSE if the individual was previously healthy before NORSE (one point) and the status epilepticus (SE) was refractory to conventional anti-seizure medications (ASMs) (one point), and no etiology was identified throughout the course of the disease [12]. Additional points are obtained if the patient has prodromal fever of unknown origin (one point), absence of prodromal psychobehavioral or memory alteration (one point), absence of sustained orofacial-limb dyskinesias (one point) and symmetric diffusion weighted imaging (DWI) or T2 weighted fluid-attenuated inversion recovery (FLAIR) hyperintensities (one point) [12].

Objectives

Immune-mediated encephalitis with seizures may be a potentially treatable and reversible cause of NORSE. Therefore, our primary aim was to describe our retrospective cohort of NORSE from Stanford University Hospital and assess the timing of immunotherapy and its effect on outcome at discharge and follow-up. Our secondary aim was to apply the cryptogenic NORSE (C-NORSE) score [12] to the subjects to evaluate its utility in distinguishing C-NORSE from NORSE due to a specific etiology. Our hypothesis was that early immunotherapy correlates with better outcomes in patients with immune-mediated causes of NORSE and that the C-NORSE score may be helpful to identify cryptogenic NORSE in patients early on.

Materials and methods

This was a retrospective review of all patients presenting with NORSE at Stanford Healthcare in Palo Alto, CA January 2004 through to April 2021. Subjects were identified through review of clinical notes using the search term "new-onset refractory status epilepticus" or "refractory status epilepticus (RSE)" through the Stanford Research Repository (STARR) database. Additional cases were identified using ICD-9 and ICD-10 codes for SE and procedure codes for continuous EEG (cEEG) with ICU admission location. Review of clinical notes, transfer documentation, laboratory results, imaging, and cEEG reports were included in the analysis. Hospital length of stay and discharge location were collected from discharge summaries. A modified Rankin Score (mRS) was determined from physical therapy documentation at discharge. Follow-up clinic visits were assessed for mRS at six and 12 months after hospital discharge and at last follow-up visit at >13 months. The presence of recurrent seizures, residual cognitive impairment, psychiatric co-morbidities and driving status were assessed. Available qualitative assessment of neuropsychological status was included in the analysis.

Subjects who met the consensus definition of NORSE with available cEEG and inpatient data at all ages were included [1]. Cases with a diagnosis of RSE which persisted beyond 24 hours based on cEEG were included. Patients were excluded if RSE was secondary to a structural lesion (*i.e.* glioma) or preceded anoxic brain injury or if the patient had posterior reversible encephalopathy syndrome (PRES) or a metabolic cause was identified within the first 72 hours of hospitalization. Patients with an underlying diagnosis of epilepsy at presentation were excluded.

Diagnostic criteria for autoimmune encephalitis including Hashimoto's encephalopathy based on Graus *et al*. [9] were added to the chart reviews. First-line immunotherapy was defined as corticosteroids, IVIg, and PLEX. Early immunotherapy was defined as administration of a first-line agent within seven days of presentation. All patients were assessed regarding the definition of NORSE during their hospitalization and treated according to institutional standards. A good or fair outcome was defined as an mRS score of 0-2; a poor outcome was defined as an mRS score of 3-6 [2].

C-NORSE scores were calculated for each subject, with scores ≥5 predicting a cryptogenic etiology for NORSE [12].

The Stanford University Institutional Review Board approved this study.

Statistical analysis

Analysis of all continuous variables included median and interquartile range (IQR). Categorical variables were analyzed with Fisher's EXACT Test. All statistical tests were 2-tailed and *p* values <0.05 were considered statistically significant. All statistical analyses were performed using Microsoft Excel and Jamovi.

Results

Twenty-six patients were identified, however, four patients were excluded due to etiologies determined >72 hours after presentation including glioma (*n*=1), anoxia (*n*=2) and PRES due to adrenal cancer (*n*=1). There was one patient, Case 17, who was presumed to have anti-NMDAR encephalitis but was serum Ab-negative; CSF Abs were not tested, therefore the patient was excluded.

Twenty-one patients met the inclusion criteria in the study period, 2004-2021 (*table 1*). The median length of stay was 30 days (IQR: 18-67). All patients received immunotherapy. Eleven patients were transferred from an outside hospital for tertiary level of care (52%). The median time to hospital transfer was five days (IQR: 4-9.5). Median age was 25 years old (IQR: 18-42), and 33% of patients were female. Fever was present prior to symptoms in 11 patients (52%), only in C-NORSE patients. Half of the patients presented with a psychiatric prodrome including psychosis (*n*=4; 19%), agitation (*n*=6; 29%), and cognitive changes (*n*=1; 5%).

Eighteen out of 21 (86%) were deemed to have C-NORSE; three out of 21 (14%) were diagnosed with immune-mediated NORSE with a named Ab syndrome (*table 2*).

Laboratory results

Serum autoimmune/paraneoplastic Ab panels were tested for all patients. Three of 21 (14%) patients were found to have clinically significant and neural-specific positive Abs (reactive to leucine-rich glioma inactivated 1 [LGI-1]; *n*=1 and anti-N-methyl-D-aspartate receptor [NMDA-R]; *n*=2). Four additional patients were found to have low levels (<20 nmol/L) of glutamic acid decarboxylase (GAD65) Ab and two patients had low levels of thyroglobulin Ab; none were thought to be clinically significant and did not meet criteria for Hashimoto's encephalopathy.

CSF was obtained in all patients (*n*=21). CSF pleocytosis (WBC >5) was found in 11 patients (52%), with median WBC of 13 (IQR: 11-15). CSF Ab panels were tested in 10 cases and two were positive for NMDA-R Ab. Oligoclonal bands were tested for 16 patients, and positive in four patients (19%).

Imaging

All patients received neuroimaging and multimodal brain MRI was normal in a minority of patients (*n*=4, 19%). Symmetric DWI or T2-weighted FLAIR hyperintensities suggestive of limbic encephalitis were found in 11 (61%) C- NORSE subjects. In 4/18 (22%) cryptogenic cases, there were focal, asymmetric, non-enhancing T2 lesions. One cryptogenic case had increased arterial spin-labeling (ASL) MRI perfusion with frontal lobe NCSE. Two cryptogenic cases demonstrated focal volume loss.

Two out of three immune-mediated NORSE cases had abnormal MRI scans with asymmetric T2 lesions which involved the frontal, anteromesial temporal or insula regions. The LGI-1 patient developed focal right caudate head and hippocampal atrophy.

Pattern of status epilepticus (SE)

All patients presented with convulsive SE, or SE with prominent motor symptoms; none presented with non-convulsive SE [13]. Focal SE was found in 13/21 patients (62%). A generalized SE pattern was noted in 3/21 patients (14%). A combined focal and generalized pattern was recorded in 5/21 (24%). Median duration of SE was 157 hours (IQR: 96-301).

C-NORSE performance

C-NORSE scores were calculated for all patients (*table 2*). A C-NORSE score ≥5 was obtained in 12/18 (67%) of the cryptogenic NORSE patients and none of the immune-mediated NORSE patients had a C-NORSE score >5.

Treatment

The median number of ASMs required to control SE was five (IQR 4-6). All patients received first-line immunotherapy including high-dose corticosteroids (*n*=21, 100%), IVIg (*n*=17, 81%), and PLEX (*n*=13, 59%) (*table 2*). Median timing to first immunotherapy was seven days after presentation (IQR: 5-7; range: 2-45 days). Second immunotherapy was initiated at a median of 14 days (IQR: 9-28). Third immunotherapy was given at a median of 31 days (IQR: 20-40) (*figure 1*). Second-line immunotherapy was administered in 6/21 (29%) of patients with rituximab, cyclophosphamide, mycophenolate mofetil or azathioprine. One C-NORSE patient was managed with long-term immunotherapy after discharge because weaning trials of

▼ **Table 1.** Clinical characteristics of cohort.

	Cryptogenic NORSE	Immune-mediated NORSE
Demographics (*n*=21)	*n*=18	*n*=3
Age: median	25	27
Female: *n* (%)	5 (28%)	2 (67%)
Transferred from outside hospital: *n* (%)	10 (56%)	1 (33%)
Time to hospital transfer (days): median	5	5
Presentation (*n*=21)		
Fever: *n* (%)	11 (61%)	0
Psychiatric prodrome: *n* (%)	7 (39%)	3 (100%)
Psychosis: *n* (%)	1 (6%)	3 (100%)
Agitation: *n* (%)	6 (33%)	0
Status epilepticus (SE) classification (*n*=21)		
Convulsive (prominent motor)	17 (94%)	3 (100%)
Non-convulsive	1 (5%)	0
EEG findings		
Duration of SE: hours, median (IQR)	191	70
Focal SE: *n*(%)	12 (67%)	1(5%)
Generalized SE *n*(%)	3 (17%)	0
Both: *n*(%)	3 (17%)	2 (11%)
Number of ASMs to control SE, median (IQR)	5.5	4
Laboratory testing (*n*=21)		
CSF (*n*=21)	9 (50%)	2 (67%)
Pleocytosis WBC >5: *n* (%)	13	18
WBC count: median (IQR)	2/13 (15%)	2 (67%)
CSF oligoclonal bands: *n* (%)	7 (39%)	3 (100%)
CSF Ab tested	0	2 (67%)
CSF Ab positive		
Serum Ab testing (*n*=21)		
Any positive Ab: *n* (%)	6 (33%)	3 (100%)
Clinically significant antibody: *n* (%)	0	3 (100%)
LGI-1 Ab	0	1
NMDA-R Ab	0	2
Clinically insignificant Ab: *n* (%)	6 (100%)	0
GAD-65 (<20 nmol/L)	4 (22%)	0
Thyroglobulin	2 (11%)	0
Brain MRI (*n*=21)		
Abnormal: *n* (%)	14 (78%)	3 (100%)
Symmetric DWI or T2/FLAIR hyperintensities	11 (61%)	0

▼ **Table 2.** C-NORSE scores with respect to diagnosis and Ab status.

C-NORSE score	Diagnosis	Age	Sex	Ab status	First-line immunotherapy (IV steroids, IVIg, PLEX)	Second-line immunotherapy
2	Immune	28	Male	LGI-1	Steroids, IVIg	None
2	Immune	20	Female	NMDA-R	Steroids, IVIg	Rituximab
3	Cryptogenic	25	Male	Negative	Steroids, PLEX	None
4	Immune	33	Female	NMDA-R	Steroids, IVIg, PLEX	None
4	Cryptogenic	18	Male	Thyroglobulin*	Steroids, IVIg	None
4	Cryptogenic	20	Male	Negative	Steroids, PLEX	None
4	Cryptogenic	30	Female	Thyroglobulin*	Steroids	None
4	Cryptogenic	31	Male	Negative	Steroids, IVIg, PLEX	None
4	Cryptogenic	53	Female	Negative	Steroids, IVIg, PLEX	None
5	Cryptogenic	15	Female	Low titer GAD-65	Steroids, IVIg, PLEX	None
5	Cryptogenic	19	Male	Negative	Steroids, IVIg, PLEX	Rituximab
5	Cryptogenic	42	Female	Negative	Steroids, IVIg, PLEX	None
5	Cryptogenic	58	Male	Low titer GAD-65	Steroids, IVIg, PLEX	None
5	Cryptogenic	60	Male	Negative	Steroids, IVIg	Mycophenolate mofetil, azathioprine
5	Cryptogenic	71	Male	Negative	Steroids, IVIg	None
6	Cryptogenic	6	Male	Negative	Steroids, IVIg	Cyclophosphamide
6	Cryptogenic	6	Male	Negative	Steroids, IVIg	None
6	Cryptogenic	9	Male	Negative	Steroids, IVIg, PLEX	Cyclophosphamide
6	Cryptogenic	10	Male	Low titer GAD-65	Steroids, IVIg, PLEX	Rituximab
6	Cryptogenic	25	Male	Negative	Steroids, IVIg, PLEX	None
6	Cryptogenic	46	Female	Negative	Steroids	None

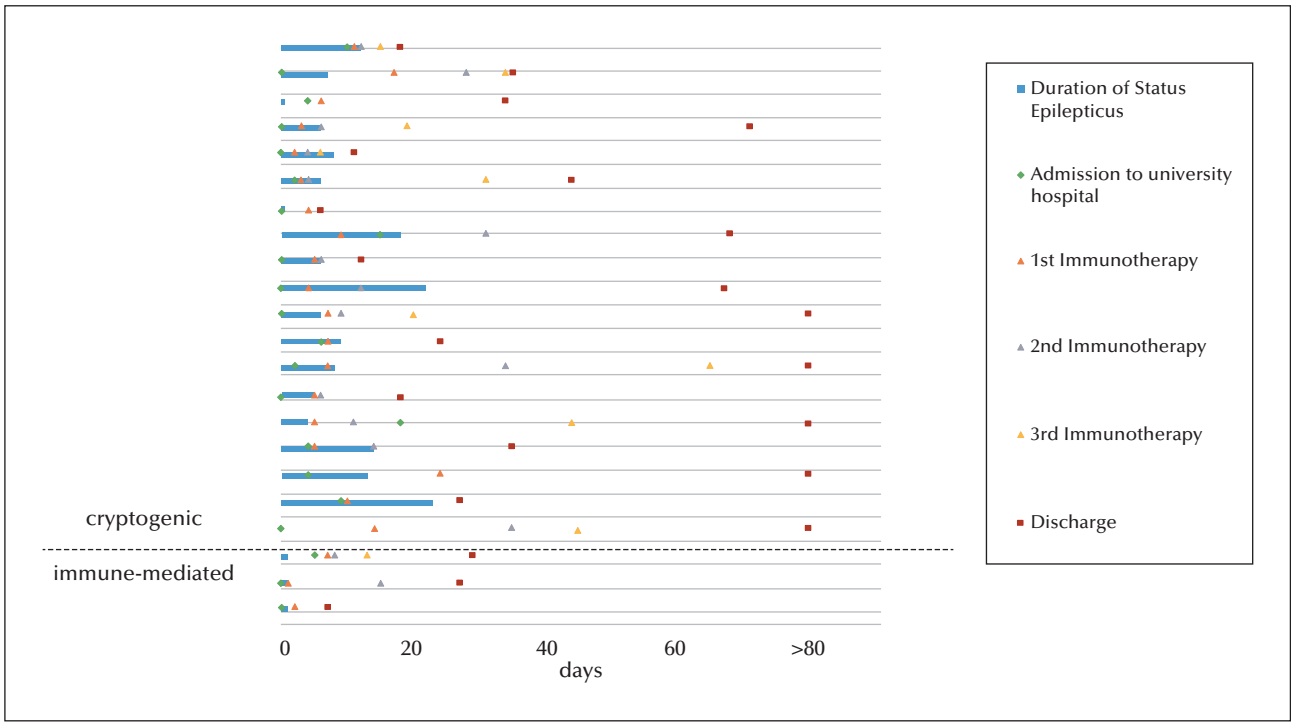
*Patients did not meet clinical criteria for Hashimoto's encephalitis. All GAD-65 levels were clinically insignificant <20 nmol/L.

steroids lead to relapses of MRI abnormalities and seizures. Rituximab was continued for two additional infusions after discharge in one patient with anti-NMDAR encephalitis.

Timing of immunotherapy was calculated based on day of presentation to medical care. Seventeen patients received early immunotherapy (81%). Timing of late immunotherapy ranged from 8-45 days from initial presentation in five patients. There was no statistically significant difference in mRS outcomes at hospital discharge or at six months of follow-up for early or late immunotherapy. There was no statistically significant difference in length of stay for early (mean: 43 days; SD: 35) compared to late immunotherapy (mean: 62 days; SD: 67), $p = 0.37$.

Outcomes

Three patients were discharged home (14%). Ten patients were discharged to an acute rehabilitation unit (48%). Six patients were transferred to the care of an outside hospital (29%). Two patients (9%) were deceased at the time of discharge (*table 3*). Favorable outcomes (mRS: 0-2) at hospital discharge were achieved in 3/21 (14%). Among the C-NORSE patients, an mRS score of 0-2 was achieved in 7/11 (64%) at six



■ **Figure 1.** Timeline of immunotherapy with respect to NORSE etiology.

months, 9/11 (82%) at 12 months and 8/10 (80%) at the last follow-up visit at >13 months. Among the immune-mediated NORSE patients, all patients (3/3; 100%) achieved a favorable outcome at six months, 2/2 (100%) at 12 months and 2/2 (100%) at the last follow-up visit at >13 months.

Follow up data was available for 15 patients (*table 3*). Median follow-up time was 4.5 years for the C-NORSE patients and 2.5 years for the immune-mediated NORSE patients. An occult malignancy, teratoma, was discovered in one anti-NMDAR encephalitis patient. Recurrent seizures were noted in 11/15 patients (73%) and 12/15 (80%) were taking ASMs; the median number of ASMs was three (IQR: 0-4) among C-NORSE patients and one (IQR: 1-3) among immune-mediated NORSE patients. The ketogenic diet was continued in 2/12 (16%) C-NORSE patients. Two C-NORSE patients had an implanted neuromodulation device for drug-resistant epilepsy; one had a vagus nerve stimulator and one had responsive neurostimulation. Follow-up cognitive outcomes were available for 12/20 (60%) patients through formal neuropsychological testing (*n*=8) or bedside mini-mental status exam or Montreal cognitive assessment (*n*=4). Eight patients (67%) were found to have cognitive impairment; four patients (33%) had normal cognitive function including one patient who enrolled in graduate school following recovery.

Psychiatric co-morbidities developed in 6/12 (50%) cryptogenic patients: depression (*n*=4), depression and suicidality (*n*=2), psychogenic non-epileptic events (*n*=1), and attention deficit hyperactivity disorder (ADHD) (*n*=1). Two patients were subsequently psychiatrically hospitalized. There were no subsequent psychiatric diagnoses for the three immune-mediated patients.

Two cryptogenic patients were noted to be driving and one NMDA patient was driving at the time of the last follow-up visit.

Discussion

This is a descriptive, retrospective cohort of Stanford NORSE patients. Our cohort was predominantly C-NORSE (86%) and only 3/21 (14%) were discovered to have immune-mediated NORSE with a named Ab syndrome, which is a smaller proportion than that described in the literature [2]. We demonstrate that early empiric use of immunotherapy is feasible and commonly practiced at our institution, with 81% of patients receiving immunotherapy in the first week after presentation. However, because of the small

▼ **Table 3.** Outcomes.

	Cryptogenic NORSE	Immune-mediated NORSE
Hospital characteristics		
Length of stay: median (days)	33	24
Discharge destination: *n* (%)		
Home	1 (6%)	2 (67%)
Rehabilitation	10 (56%)	0
Outside hospital	5 (26%)	1 (33%)
Deceased	2 (11%)	0
Modified Rankin scale (mRS) at discharge: *n* (%)		
mRS: 6 death	2 (11%)	0
mRS: 5	4 (22%)	1 (33%)
mRS: 4	8 (44%)	0
mRS: 3	2 (11%)	1 (33%)
mRS: 2	2 (11%)	1 (33%)
mRS: 0-1	0	0
Favorable outcome (mRS: 0-2)	2 (11%)	1 (33%)
mRS at follow-up		
mRS: 0-2 at the 6-month follow-up visit	7/11 (64%)	3/3 (100%)
mRS: 0-2 at the 12-month follow-up visit	9/11 (82%)	2/2 (100%)
mRS: 0-2 at the last follow-up visit (>13 months)	8/10 (80%)	2/2 (100%)

number of cases and the heterogeneity of etiologies, early immunotherapy did not show a statistically significant effect on outcomes of NORSE patients. Although NORSE is increasingly recognized, it remains a rare disease with high mortality and therefore conducting randomized controlled trials would pose both recruitment and ethical challenges. NORSE patients are subjected to many therapies using a non-standardized approach. Therefore, it is challenging to determine whether patient outcome is influenced by individual or combination therapies or whether patient outcome reflects the natural history of the disease process.

The mortality rate of 2/21 (10%) in our study is lower than that reported in prior reports of NORSE mortality, ranging from 22-30% [2]. Among the patients in our cohort who survived hospitalization, long-term follow-up of our NORSE cohort demonstrated that 12/21 (57%) achieved good mRS (0-2) scores which is slightly better compared to prior reports of 39-42% [14]. However, the mRS score does not fully capture cognitive deficits that the patients may suffer from at discharge and at follow-up. Of the 14 patients who had long-term 12-month follow-up, 11 (78%) had a good outcome (mRS 0-2), however, 12/15 (80%) required ASMs, 8/12 (67%) had persistent cognitive impairment, and 6/11 (55%) C-NORSE patients developed psychiatric co-morbidities. The longer-term outcome mirrors findings from a prior report in the literature [14].

Many studies in the literature suggest that early immunotherapy for autoimmune encephalitis and SE leads to better cognitive and functional outcomes [11, 15]. Data on the timing of immune therapies are only available in sufficient numbers for the two most common neuronal cell surface Ab syndromes: anti-NMDAR and anti-LGI-1 encephalitides. Observational studies on anti-NMDAR encephalitis have shown that early immunotherapy (<40 days) in non-paraneoplastic patients is significantly correlated with good outcome (mRS 0-2) [16]. Additionally, those with second-line immune therapies in the cohort of Titulaer *et al*. did significantly better than those without. Among anti-LGI-1 encephalitis patients, early immunotherapy has been correlated with good mRS outcome [17, 18]. Consistent with published literature, the two anti-NMDAR patients in our cohort received early immunotherapy (2-7 days) and achieved good outcomes (mRS: 0-2). Khawaja and colleagues reported on a pooled analysis of NORSE cases at their institution, compared to several case series in the literature, suggesting a statistically significant difference in favorable outcomes in patients (19/45 [42%]) treated with immunotherapy compared to those who were untreated (10/49 [20%]) [19]. Compared to our cohort, Khawaja *et al*. had a

larger proportion of patients with detected Ab (7/11 [64%]) and only 3/11 with either C-NORSE or incomplete evaluations. However, one patient had positive anti-VGKC Ab, however, this was not confirmed and the levels of titers from positive anti-GAD65 Ab patients (*n*=3) were not detailed. Therefore, it is unclear whether these positive Abs were clinically significant. Despite these limitations for comparison, all patients in our cohort received immunotherapy and 12/21 (57%) had a favorable outcome with an mRS score of 0-2 at the last follow-up visit, which is similar to Khawaja *et al.*'s pooled analysis. These results are suggestive of a potential role for immunotherapy in NORSE cases, however, the evidence remains Class IV.

There is a paucity of published data on the timing of immunotherapy in NORSE patients [19, 20]. Current proposed treatment strategies for NORSE encourage early initiation of immunotherapy after preliminary studies have ruled out infectious etiologies or structural lesions. There are a handful of case reports and series hinting that intensive or early immunotherapy can lead to a favorable outcome for NORSE [21-23]. Based on a case series by Gall *et al.*, 3/5 NORSE cases were treated with IV steroids and IVIg, and the authors asserted that early immunotherapy was associated with good outcomes. They described one patient with steroids administered on Day 12 and IVIg on Day 18, however, the timing in the other two cases was not detailed [8].

Some authors have described clinical features, distinguishing between cryptogenic and immune-mediated encephalitis as etiologies of RSE, to identify autoimmune patients who are known to have benefited from early immunotherapy. In our small cohort, the C-NORSE score of $\geq$5 had a fair capture rate of 67% and was 100% specific. Recent work by Yanagida *et al.*, based on 81 patients with NORSE, including 33 with C-NORSE, revealed a higher sensitivity of 93.9% (95% CI: 0.87-0.94) and specificity of 100% (95% CI: 0.95-1.00) [24]. The differences in sensitivity and specificity calculation are likely due to the population studied as well as a lower number of patients in our cohort. Although C-NORSE patients may respond to immunotherapy, the C-NORSE score may help to select patients for early, aggressive immunotherapy [12]. Lin *et al.* suggested that autoimmune SE can be distinguished on clinical grounds and suspected in patients with "younger age, female sex, psychosis, NCSE, and super RSE" [25]. The antibody prevalence in epilepsy (APE) and response to immunotherapy in epilepsy (RITE) scores are also predictive models to clinically identify cases with possible immune-mediated causes of epilepsy amenable to immunosuppression [26].

Because NORSE is rare and etiologies are heterogenous, pooled data from clinical registries are needed and should be submitted to the Critical Care EEG Monitoring Research Consortium (https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc) and NORSE Institute (https://www.norseinstitute.org). No doubt, newer Abs will be discovered and perhaps precision medicine-targeted immunotherapy to specific antigen types may become first-line treatment in the future. The anti-inflammatory effects of the ketogenic diet or newer agents, such as anakinra interleukin-1 receptor antagonist, need to be evaluated in prospective controlled studies [5, 11, 20, 27].

This study has several limitations, being a retrospective review of a rare disease entity in a single university hospital setting without a control group, as all patients received immunotherapy. Only a small number of patients were identified, spanning a prolonged period of 17 years. Older cases had some missing data and Ab panels were more limited. Although CSF was obtained for all patients, CSF Ab panels were tested in less than half of the patients. Additionally, the CSF Ab panel only included $GABA_B$ receptor Ab in 2015 and did not include $GABA_A$ receptor Ab. There is no established "early" versus "late" immunotherapy timelines in the literature. We defined early immunotherapy as "less than" seven days based on expert opinion for this study. Finally, follow-up data was not available for all patients and our long-term results were likely influenced by selection bias.

Conclusions

Despite the limitations of this study, we describe a retrospective cohort of NORSE patients at our institution. Our results suggest that the use of the C-NORSE score may help identify C-NORSE which may influence the use of immunotherapy. Furthermore, we demonstrate that early immunotherapy is feasible. Among the hospital survivors in our cohort, 57% achieved good outcomes at the last follow-up visit. More studies are needed to assess the effects of various treatments, such as immunotherapies, and their timing on the outcome of subsets of NORSE patients. Pooled analyses with case-matched controls may further elucidate the utility of early immunotherapy in NORSE patients prior to receiving confirmation of Ab status. Future studies may utilize the C-NORSE score to select patients for early immunotherapy. Until these studies are performed, questions surrounding both the timing and escalation of immunotherapy in patients with NORSE remain unanswered. ■

Key points

- New-onset refractory status epilepticus (NORSE) is an uncommon entity with a high mortality rate.
- There is no established NORSE treatment protocol.
- Early immunotherapy is feasible: 81% of NORSE patients received a first-line agent within seven days of presentation at our institution.
- There was no statistically significant effect of early immunotherapy on mRS outcomes.
- C-NORSE scores $\geq$5 were achieved in 67% of cryptogenic cases and scores < 5 in all three immune-mediated cases.

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) Cases of NORSE are:
A. common and etiologies are readily identified
B. rarely treated with immunotherapy at Stanford
C. have diverse etiologies but are most commonly cryptogenic
D. respond readily to conventional anti-seizure medications
E. are treated according to standardized protocols

(2) A high cryptogenic-NORSE (C-NORSE) score $\geq$5:
A. implies an autoimmune etiology
B. helps identify cryptogenic NORSE
C. predicts responsiveness to immunotherapy
D. predicts favorable outcome (mRS score: 0-2)
E. requires second-line immunotherapy

(3) Early immunotherapy for patients with NORSE:
A. is only beneficial in cryptogenic cases
B. is only beneficial in immune-mediated cases
C. is defined as treatment within 14 days
D. was shown to correlate with good outcomes (mRS score: 0-2)
E. was not shown to have an effect on mRS outcomes

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.