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RESEARCH ARTICLE

Clinical outcomes among initial survivors of cryptogenic new-onset refractory status epilepsy (NORSE)

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Abstract

Objective: New-onset refractory status epilepticus (NORSE) is a rare but severe clinical syndrome. Despite rigorous evaluation, the underlying cause is unknown in 30%–50% of patients and treatment strategies are largely empirical. The aim of this study was to describe clinical outcomes in a cohort of well-phenotyped, thoroughly investigated patients who survived the initial phase of cryptogenic NORSE managed in specialist centers.

Methods: Well-characterized cases of cryptogenic NORSE were identified through the EPIGEN and Critical Care EEG Monitoring Research Consortia (CCEMRC) during the period 2005–2019. Treating epileptologists reported on post-NORSE survival rates and sequelae in patients after discharge from hospital. Among survivors >6 months post-discharge, we report the rates and severity of active epilepsy, global disability, vocational, and global cognitive and mental health outcomes. We attempt to identify determinants of outcome.

Results: Among 48 patients who survived the acute phase of NORSE to the point of discharge from hospital, 9 had died at last follow-up, of whom 7 died within 6 months of discharge from the tertiary care center. The remaining 39 patients had high rates of active epilepsy as well as vocational, cognitive, and psychiatric

comorbidities. The epilepsy was usually multifocal and typically drug resistant. Only a minority of patients had a good functional outcome. Therapeutic interventions were heterogenous during the acute phase of the illness. There was no clear relationship between the nature of treatment and clinical outcomes.

Significance: Among survivors of cryptogenic NORSE, longer-term outcomes in most patients were life altering and often catastrophic. Treatment remains empirical and variable. There is a pressing need to understand the etiology of cryptogenic NORSE and to develop tailored treatment strategies.

KEYWORDS

cryptogenic, new-onset refractory status epilepticus (NORSE), outcomes

1 | INTRODUCTION

New-onset refractory status epilepticus (NORSE) is defined as the clinical presentation of new onset of refractory status epilepticus in a person without pre-existing epilepsy or other neurologic disorder.[1] A cause is established in 60%–70% of adult cases with the most common recognized etiology being antibody-mediated encephalitis.[2–4] Other causes include central nervous system (CNS) infections, genetic disorders, metabolic derangements, or toxins. Despite rigorous testing, the cause of or trigger for NORSE is often not found; consequently a diagnosis of "cryptogenic" NORSE[1,5] is typically assigned. This rare syndrome often results in devastating consequences. The majority of published accounts focus on short outcomes after NORSE.[2] Our study describes the natural history and long-term clinical outcomes in a cohort of patients with cryptogenic NORSE who were cared for in international academic medical centers with epilepsy expertise.

Key points

- Cryptogenic new-onset refractory status epilepticus (NORSE) is associated with severe enduring clinical consequences among survivors.
- Nineteen percent of patients died after discharge from hospital—usually within 6 months—and only 4% of patients made a full neurological recovery.
- No clear relationship between nature of treatment and clinical outcomes was identified.

2 | METHODS

2.1 | Patient cohort

We performed a retrospective cohort study of patients admitted under the care of epileptologists or neuro-intensive care physicians across the EPIGEN and Critical Care EEG Monitoring Research Consortia (CCEMRC). Only people with follow-up for >6 months for survivors were included, some of whom have been reported previously.[2] All individuals included met current NORSE diagnostic criteria[1] and were managed in tertiary care neuroscience centers with epilepsy expertise, neuro-intensive care expertise, and acute electroencephalography (EEG) capability. The study captured patients from 2005 to 2019. Before assigned a diagnosis of *cryptogenic* NORSE, all patients underwent extensive testing, focused particularly on exclusion of infectious, paraneoplastic, immune-mediated, and genetic etiologies. Patients were excluded from the analysis if the underlying cause was identified after the acute phase of NORSE, particularly occult neoplasia.

2.2 | Data collection

The data collected from each contributing center were de-identified. D.C. developed a detailed data collection document in Excel format. Co-authors populated the document with details from each patient in their center. The data collected included demographics, internal medical and neurological history, epilepsy risk factors, prodromal symptoms, diagnostic test results including EEG and imaging findings, status epilepticus characteristics, intensive care unit (ICU) length of stay admission and length of hospital admission, duration and type of therapies antiseizure medications (ASMs), immunosuppressant therapies, continuous intravenous anesthetic drugs (CIVADs), ketogenic diet, and other medications or therapeutic strategies. Because the data were retrospective and collected from medical charts, we focused on crude cognitive, mental health, and vocational outcomes in order to get a

general sense of the real-world impact among survivors of the illness.

Functional outcomes were documented using the modified Rankin score (mRS) at least 6 months after discharge, categorized as favorable (mRS 0–2; independent for all activities of daily living), unfavorable (mRS 3–5; dependent for some to all activities of daily living), and death (mRS 6). Vocational, cognitive, and mental health outcomes including ability to return to school or work, persisting cognitive impairment, and behavioral issues were recorded.

In addition, we collected information regarding the presence and type of post-NORSE epilepsy including seizure frequency (daily seizures, seizures occurring on a weekly basis, seizures occurring on a monthly basis, seizures occurring less often than monthly, seizure freedom), number of ASMs, and video-EEG findings, where available.

2.3 | Statistical analysis

Data were reported as count (frequency) or median (interquartile range [IQR]). Univariate analyses were performed comparing the favorable vs the unfavorable and deceased groups with the Mann–Whitney or Fisher exact tests. Correlations between continuous variables were performed with Spearman's rho. A false discovery rate–corrected two-tailed p-value <.05 was considered statistically significant. Because the number of patients in the cohort is relatively small, multivariate analysis was not conducted.

3 | RESULTS

Forty-eight patients were identified from 10 centers. The centers were based in North America (New York City $n=11$, New Haven $n=6$, Boston $n=3$, Alabama $n=2$), Europe (Dublin $n=5$, Cork $n=6$, Oxford $n=6$, Brussels $n=4$), and Australia (Melbourne $n=5$). Of these, 21 cases have been partially reported previously.[2] The patients were predominantly female (28/48; Table 1). Median age was 30 (24–54) years. Only five patients (10%) had a family history of epilepsy or had a documented risk factor for epilepsy. None of the patients had a major premorbid mental illness or pre-existing cognitive impairment.

3.1 | Acute phase

Of the 48 patients, 38 (79%) had a documented prodromal illness within 2 weeks of the onset of seizures. In 24 (50%) patients the prodrome consisted of a "flu-like" illness with myalgias, fever, and fatigue. A small number of patients had prominent respiratory, gastrointestinal symptoms, or behavioral or cognitive changes before the onset of seizures. After the onset of status epilepticus, patients had protracted clinical courses with median lengths of stay in ICU and in hospital of 28 (IQR 16–59) days and 50 (IQR 27–73) days, respectively. The status epilepticus was super-refractory in 40 patients (83%) and required a median of 2 (2, 3) CIVADs, including ketamine in 20 (42%) and thiopental/pentobarbital in 20 (42%). Five patients were trialed on the ketogenic diet during the acute phase of their illness.

TABLE 1 Demographics, clinical course, and therapeutic interventions during acute phase.

	N = 48 (% of total)
Female sex	28 (58)
Mean age (years)	30 (24–54)
Risk factors for epilepsy	5 (10)
Family history of epilepsy	3 (6)
Remote history of febrile seizures or active epilepsy	1 (2)
Other	1 (2)
Prodromal symptoms (within 2 weeks of NORSE onset)	38 (79)
Fever	24 (50)
Headache	12 (25)
Symptoms suggestive of respiratory tract infection	9 (19)
Symptoms suggestive of gastrointestinal tract infection	13 (27)
Behavioral or cognitive change	8 (17)
Duration of ICU stay, days (IQR)	28 (16–59)
Duration of hospital stay, days (IQR)	50 (27–73)
Super-refractory status epilepticus, no. (%)	40 (83)
Number of CIVADs received, no. (range)	2 (2–3)
Use of thiopental/pentobarbital, no. (%)	20 (42)
Use of ketamine, no. (%)	20 (42)
Immune therapies during the acute phase, no. (%)	38 (79)
Steroids	37 (77)
IVIG	20 (42)
Plasma exchange	19 (40)
Rituximab	4 (8)
Ketogenic diet	4 (8)

Note: Data are presented as count with either frequency (%) or median duration (IQR).

Abbreviations: CIVADs, continuous intravenous anesthetic drugs; ICU, intensive care unit; IQR, interquartile range; IVIG, intravenous immune globulins.

Thirty-eight patients (79%) were treated with at least one immunosuppressant or immunomodulatory agent during their clinical course, most often steroids. Details are reported in Table 1. Overall, 12 patients (25%) received steroids only and 25 (52%) received steroids and at least one other immunomodulatory drug. None of the patients were treated with neurostimulation, anakinra, or tocilizumab. Patients with a longer stay in the ICU received more CIVADs (Spearman's rho: .49; $p = .005$), as well as more immune therapies (Spearman's rho: .61; $p = .01$).

During the acute phase of the illness, all patients underwent EEG monitoring and magnetic resonance imaging (MRI), as summarized in Table 2. All EEG studies (100%) were markedly abnormal with frequent epileptiform or periodic abnormalities. Discrete seizures or continuous ictal activity was observed in individual EEG recordings in 38 patients (79%). Repeated or continuous EEG recordings revealed electrographic seizure activity in all patients. Almost half (48%) of patients had abnormal MRI findings in the acute phase, mostly involving the hippocampus, often bilaterally. At least one lumbar puncture was performed in each patient, with a pleocytosis (white cell count >5/mm^3) observed in 26 (54%).

TABLE 2 Findings from diagnostic tests during the acute phase of illness (N = 48).

Diagnostic modality	Number (%)
Abnormal brain MRI, no. (%)	22 (46)
FLAIR abnormalities	20 (42)
DWI abnormalities	15 (31)
Bilateral abnormalities	12 (25)
Neocortical abnormalities	4 (8)
Hippocampal abnormalities	14 (29)
Thalamic abnormalities	4 (8)
Basal ganglia abnormalities	3 (6)
Claustrum abnormalities	2 (4)
Abnormal CSF, no. (%)	37 (77)
Cell count (cells/mm^3)	7 (1–14)
Cell count >5/mm^3	26 (54)
Cell count >50/mm^3	4 (8)
Abnormal 30 min EEG studies or continuous EEG, no. (%)	48 (100)
Sporadic epileptiform discharges	13 (27)
LPDs or BIPDs	12 (25)
Discrete electrographic seizures	26 (54)
Electrographic SE	12 (25)
Bilateral/multifocal epileptiform abnormalities	26 (54)

Note: Data are presented as count (frequency) and percentage of total.

Abbreviations: BIPDs, bilateral independent periodic discharges; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; LPDs, lateralized periodic discharges; MRI, magnetic resonance imaging; SE, status epilepticus.

3.2 | Long-term follow-up

From the cohort of 48 patients who survived the acute phase and were discharged from hospital, 9 (19%) died after discharge (median time 4.5 months). Of these, seven patients died within 6 months of discharge. Long-term functional outcomes in survivors were obtained at a median of 23 (IQR: 11–39; range: 6–101) months after discharge from hospital (Table 3). Among patients who survived for 6 months post

TABLE 3 Functional, cognitive, mental health and epilepsy outcomes after acute phase of NORSE.

	Number (% or range)
Time to last follow-up assessment (months)	23 (11–39)
Functional outcome (mRS)	
Favorable (0–2)	18 (38)
Unfavorable (3–5)	21 (44)
Death (6)	9 (19)
Enduring self-reported cognitive impairment ($N = 39$ survivors)	30 (77)
Enduring documented mental health difficulties ($N = 39$ survivors)	21 (554)
Alive and able to return to education (of 7 patients in school before illness)	5 (71)
Alive and able to return to work (of 30 patients in employment before illness)	7 (23)
Seizure burden at time of follow-up (among 39 survivors)	
None	8 (22)
<1 seizure per month	8 (19)
≥1 seizure per month but <1 seizure per week	12 (32)
≥1 seizure per week	11 (27)
Mean number of prescribed antiseizure medications at follow-up	3 (2–4)
EEG and video-EEG findings ≥6 months after acute phase (of 35 patients recorded)	
(uni) Focal epileptiform abnormalities	21 (68)
Bilateral/multifocal epileptiform abnormalities	14 (45)

Note: Data are presented as count with frequency (%) or median (interquartile range).

Abbreviations: EEG, electroencephalography; mRS, modified Rankin scale.

discharge, only two patients (4%) recovered fully (mRS 0). Twenty-one patients (44%) had an unfavorable outcome, whereas 18 patients (38%) had a favorable outcome. Of the seven patients who were attending school prior to NORSE, five resumed formal education. Of the 30 patients who were professionally active prior to NORSE, only seven resumed work within the time of our data capture. The majority of survivors had significant enduring cognitive (31/39; 79%) or psychiatric comorbidities, particularly anxiety or depressive disorder (21/39; 54%).

None of the investigated variables were associated significantly with functional outcome including older age at presentation (Table 4). The duration of ICU stay did not seem to predict clinical outcome, although the study was underpowered to reliably prognosticate. The longest duration of ICU stay that was associated with favorable outcome (mRS 1 or 2) was 72 days and the longest duration of ICU stay associated with full recovery was 28 days. All 39 survivors were prescribed ASMs at last follow-up, with a median of 3 (range 2–4) ASMs. Only 8 (21%) of the 39 surviving patients were seizure-free for >12 months at last follow-up, with 10 (26%) having at least weekly seizures. Of the eight patients who were seizure-free at 12 months, they had been seizure-free at the point of discharge from hospital. Two patients underwent vagus nerve stimulator implantation. None of the survivors had undergone resective epilepsy surgery. Thirty-one (79%) of the 39 surviving patients underwent video-EEG monitoring to assess their ongoing post-NORSE epilepsy. All were abnormal, with epileptiform abnormalities found in 21 (54%), which were bilateral independent or multifocal in 14 patients.

4 | DISCUSSION

We describe outcomes in a retrospective case series of a comparatively large cohort of 48 patients with cryptogenic NORSE from multiple international academic medical centers. This study focused on "real life" longer outcomes after discharge from hospital. The cohort's demographics, acute clinical presentation, and subsequent hospital course are in keeping with prior reports where prolonged ICU stays and super-refractory status epilepticus is the norm.[2,6–10] Consistent with previous studies, this cohort were typically young, neurologically healthy, and without prior risk factors for development of epilepsy.

Previous studies have focused on in-hospital survival rates and short-term functional and epilepsy outcomes, with median duration <12 months.[2,10,11] This study describes real-world outcomes after a median follow-up of 23 months (range 6–101 months), thus providing a longer-term view of what outcomes can be expected in patients diagnosed with NORSE.

Previous studies have reported inpatient mortality rates of 25%–50%, typically in the acute phase of the illness.[2,7,12,13] There have been reports of improvements in disease status after discharge in this population.[2] In comparison, we found that up to 19% of patients died after discharge from hospital, and the majority within 6 months of discharge. Although only a small minority of patients in our series recovered fully (4%, $n = 2$), a third achieved favorable outcome with a return to education or work. A recent case series of 26 adults reported that 6 patients (23%) had good or fair outcome (mRS 0–3) at hospital discharge. Of the patients with long-term follow-up data (median 9 months, interquartile range 2–22 months), 12 patients

TABLE 4 Potential determinants of outcome.

	Favorable outcome ($N = 18$)	Unfavorable outcome or death ($N = 30$)	*p*-value (uncorrected)
Age	28 (22–38)	38 (26–55)	.07
Prodromal symptoms	15 (83)	23 (77)	.58
Prodromal fever	9 (50)	15 (50)	>.99
Duration of ICU stay	25 (20–40)	40 (16–73)	.20
Super-refractory status epilepticus	14 (78)	26 (87)	.42
Number of CIVADs used	2 (2–3)	2 (2–3)	.54
Number of immune therapies used per patient	4 (1–5)	3 (1–5)	.62
Use of ketogenic diet	2 (11)	3 (10)	.90
Bilateral MRI abnormalities	3 (17)	9 (30)	.37
CSF lymphocyte count (cells/mm^3)	7 (2–10)	6 (1–17)	.75
Bilateral/multifocal acute EEG abnormalities	12 (67)	14 (47)	.11

Note: Data are presented as count (frequency) or median (interquartile range).

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; ICU, intensive care unit; MRI, magnetic resonance imaging; SE, status epilepticus.

(71%) had mRS 0–3[10]. Another case series with 11 patients after a median follow-up of 11 months reported poor outcomes (defined as mRS 4–6) in 8 patients (73%).[11] In previous studies, clinical outcomes are poorer in patients with cryptogenic NORSE when compared with NORSE with a known etiology (usually immune-mediated). Overall, as demonstrated here and previously, the chance of complete recovery after NORSE is currently low.

None of the clinical variables was significantly associated with outcome. Only older age approached significance, which is not unexpected, as age is a determinant of outcome in all causes of status epilepticus and critical illness. Patients with a longer ICU stay did not have a worse outcome, although their stay was characterized by a more severe course, as indirectly indicated by the need for more CIVADs and the use of more immune therapies. With the caveat that treatment strategies and timing were variable across institutions, the outcomes from this cohort do not provide compelling evidence that more aggressive "front-loaded" interventions are more beneficial than a step-wise ("escalating") approach to management of cryptogenic NORSE. Specifically, the number of CIVADs and number of immune therapies used were not associated with more favorable outcomes. This finding has been reported before in smaller series.[2,10,11]

Given the uncertainty about the optimal management of patients with NORSE,[14] therapeutic decisions made by treating physicians were highly variable. It is not possible to conclude from this retrospective observational study whether intensive CIVADs and immune therapies are futile in cryptogenic NORSE or if they help achieve better outcomes in more severe cases in which they are more often employed. Of note, none of the patients in the cohort received anakinra or tocilizumab, which were first reported to ameliorate the disease course after this cohort were treated. Markers of more extensive cerebral involvement and inflammation, such as cerebrospinal fluid (CSF) pleocytosis, bilateral/multifocal acute imaging, or EEG epileptiform abnormalities were not associated with worse outcomes, suggesting that they should not be used for prognostic purposes. Recent efforts to develop a standardized approach to biospecimen collection and analysis will help to clarify the potential for biomarkers to prognosticate and possibly guide therapy in NORSE.[15]

In this cohort, most survivors experience enduring long-term complications arising from their illness. Drug-resistant multifocal epilepsy requiring polytherapy appears to be a common outcome. The psychosocial impact of NORSE was severe in the majority of patients. Only a minority returned to normal employment or education. Although detailed neuropsychometric assessments were not undertaken in all survivors, cognitive difficulties were reported in a majority of the patients. A large proportion of patients (24 of 39) also reported ongoing, significant psychopathological and psychiatric complications that were not present prior to NORSE diagnosis. These findings indicate that cryptogenic NORSE survivors should receive not only epilepsy care but also comprehensive neuropsychological and neuropsychiatric counseling and social assistance.

Given the retrospective observational nature of this study, there are many limitations. Patients were managed in different centers using different treatment protocols presumably based on clinical experience and empirical approaches to refractory status epilepticus. Because cryptogenic NORSE is rare, the total number of patients included in the study was small ($n = 48$). Consequently, the study was underpowered to identify patient-related, illness-related, and treatment-related parameters that may predict clinical outcomes. The study did not differentiate between NORSE-related outcomes and iatrogenic treatment-related outcomes. Nonetheless, this large case series documents the real-world consequences of this severe monophasic neurological illness that typically affects healthy young adults. There is a pressing need for further study into this rare, but usually devastating, clinical syndrome. Specifically, the impact of empirical immunotherapy needs to be clarified, particularly in light of new insights into the role of cytokines in NORSE.[15,16] Recent efforts to consolidate expert opinion have led to consensus recommendations for the management of NORSE[17,18] and further study to re-evaluate outcomes after implementation of these recommendations will be important.

5 | CONCLUSIONS

This comparatively large retrospective study documents that approximately two thirds of patients who survive the acute phase of cryptogenic NORSE to the point of discharge from hospital will either die or have a poor clinical outcome. We did not identify any patient-, illness-, or treatment-related variable that predicted survival or clinical outcome. The study highlights the need for multidisciplinary management of patients with NORSE both during admission and subsequent to hospital discharge to manage both epilepsy and the ensuing cognitive and psychiatric comorbidities.

AUTHOR CONTRIBUTIONS

Daniel J. Costello: study conceptualization; data collection and curation; formal analysis; original draft writing and review/editing. **Elizabeth Matthews:** data collection; original draft review and editing; revised manuscript editing. **Sidra Aurangzeb:** data collection; original draft review and editing; revised manuscript editing.

Elisabeth Doran: data collection; original draft review and editing; revised manuscript editing. **Jessica Stack:** data collection; original draft review and editing; revised manuscript editing. **Robb Wesselingh:** data collection; original draft review and editing; revised manuscript editing. **Patricia Dugan:** data collection; original draft review and editing; revised manuscript editing. **Hyunmi Choi:** data collection; original draft review and editing; revised manuscript editing. **Chantal Depondt:** data collection; original draft review and editing; revised manuscript editing. **Orrin Devinsky:** data collection; original draft review and editing; revised manuscript editing. **Colin Doherty:** data collection; original draft review and editing; revised manuscript editing. **Patrick Kwan:** data collection; original draft review and editing; revised manuscript editing. **Mastura Monif:** data collection; original draft review and editing; revised manuscript editing. **Terence J. O'Brien;** data collection; original draft review and editing; revised manuscript editing. **Arjune Sen:** data collection; original draft review and editing; revised manuscript editing. **Nicolas Gaspard:** Conceptualization; data curation; formal analysis; original draft writing and review/editing; revised manuscript editing.

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CONFLICT OF INTEREST STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was not funded through any external party or agency. None of the authors have any conflict of interest to disclosure.

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