Predictors of outcome in cNORSE: hope for tomorrow

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Caring for a patient with a diagnosis of cryptogenic new-onset refractory status epilepticus (cNORSE) is one of the most challenging scenarios facing a clinician: A rare presentation in usually young and previously healthy individuals, lack of evidence and biomarkers to guide treatment, a long duration of illness complicated by status epilepticus (SE) morbidity and a hitherto unpredictable outcome with a prognosis ranging from death or severe neurodisability to, at best, survival with chronic epilepsy.

With their study, Jang *et al*[1] contribute the first predictors of outcome in cNORSE based on the duration of unconsciousness and MRI features at 3 months.

This cohort study is a subgroup analysis of patients fulfilling cNORSE criteria enrolled into a prospective observational cohort study in Korea, and albeit being retrospective, it is one of the largest cNORSE series reported to date.[2]

Jang *et al* creatively approach some of the difficulties faced by clinicians engaged in NORSE research, including the lack of consensus definitions on the duration of NORSE (here overcome by using recovery of consciousness to the ability to obey one-step commands) and on how to reproducibly quantify seizure burden and dynamics (assessing monthly seizure frequency and antiseizure medication use). As a point of criticism, better outcome scales than the modified Rankin Scale (mRS), frequently criticised for its subjective nature viewed as skewing results and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) score[3] (used for autoimmune encephalitides and including items such as dystonia and ataxia in which patients with NORSE would typically not score highly) would have been valuable, as would have including cognitive and neuropsychiatric outcomes. Despite some inherent recruitment bias, as patients were initially recruited into an autoimmune encephalitis (AE) cohort, the study convinces with thorough patient characterisation including autoimmune antibody evaluation by both cell and tissue-based assays and is laudable for standardised timing and evaluation of MRI at 3 months and good long-term follow-up (94.6% to 1 year and 83.8% for 2 years) in a challenging population. After the exclusion of cases with antibody-proven AE, the authors show that of 74 patients fulfilling cNORSE criteria at discharge, that is, not later identified to have an alternative aetiology, a remarkable 83.8% (62/74) regained consciousness reaching a point where they were able to obey one-step commands within a median duration of 30 days (14–56) with 12 (16.2%) achieving seizure freedom. Additionally, there was no significant difference in mRS outcome between those presenting with convulsive versus non-convulsive SE.

While all patients received first-line immunotherapy (steroids, intravenous immunoglobulins or both) within 8 days and 91.9% (68/74) received second-line immunotherapy with rituximab, tocilizumab or both, this paper does not provide guidance for prospective immunotherapy decisions, as not all treatments were evaluated (the frequently used anakinra being used in only five patients due to local regulatory policies), treatment groups were unmatched (baseline characteristics and time to treatment) and no treatment decisions were taken in an a priori unbiased way.

Prognostic factors to predict longer-term outcomes were evaluated through multivariate analysis. While older age (≥50 years), prolonged duration of unconsciousness (≥3 weeks) and duration of anaesthetic use (≥3 weeks) was correlated with a poor outcome (defined as mRS≥3) at 3 months, none of these factors successfully predicted 1-year outcomes post-SE onset mirroring the clinical experience of good outcomes even after many months of SE and the importance of persevering with treatment and interventions.

The main result of this study is the identification of prediction markers for 1-year outcomes at the 3-month mark: Poor 1-year outcome (defined as mRS≥3) was correlated with the presence of abnormal lesions in the mesial temporal lobe (mTL) structures and/or extra-mTL observed on the 3-month MRI and prolonged unconsciousness ≥60 days. Patients in the poor outcome group had higher rates of mTL atrophy over 2 years. This prognostic power was still valid even after adjusting for age, baseline assessment and presence of cortical atrophy in the initial MRI. MRI findings, however, were not significant in predicting seizure frequency/month at 1 and 2 years.

The mTL is the most common location of the so-called acute seizure-induced brain MRI lesions[4] and is susceptible to inflammation-induced injury,[5] but whether the hippocampal formation plays a primary role in the pathogenesis of NORSE or is secondarily involved is not yet understood. Other authors have attempted to describe pathognomonic MRI findings for both early and late phases of cNORSE[6] without finding typical evolution patterns and with a majority of MRIs reported normal in the initial phases. The strength of Jang's work is to identify four MRI patterns at 3 months correlated with different long-term outcomes. It is important to remember that the current definition of cNORSE[7] does not exclude seronegative autoimmune encephalitis (AE)[8] and indeed this study included four patients fulfilling criteria for definite autoimmune limbic encephalitis and eight patients for antibody-negative but probable AE: It is likely that different pathophysiological processes may result in a cNORSE presentation initially and one could speculate these might have different early MRI findings. This study adds that MRI at 3 months (ie, in the chronic epilepsy post-SE phase) distinguishes a subgroup of patients with worse outcomes. Whether these patients have an altogether different aetiology or whether the same disease manifests along a spectrum of severity requires further investigation. Hanin *et al* have recently reported that elevation of serum innate immunity-associated proinflammatory cytokines (IL6, CXCL8, CCL2, MIP-1alpha) are correlated with worse outcomes at intensive care unit discharge and several months after SE ended.[9] These proinflammatory cytokines have been shown to play roles in modulating neuronal excitability, mediating macrophage recruitment and neuronal damage in animal models of SE.[9] In this study, Jang *et al* report similar elevations of cytokines associated with innate immunity in patients with cNORSE but cytokine measurements were taken at different time points from presentation and into treatments, without serial sampling and should be interpreted with caution

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because it is not possible to ascertain whether proinflammatory cytokines rise as cause or consequence of seizures. Future studies should address whether cytokine levels rise transiently and whether immunotherapy alters cytokine levels and outcomes long-term.

Finally, while there is hitherto no conclusive evidence that the use of immunosuppression has reduced mortality in NORSE, typically reported to be around 10–30%,[10] in this study the 1-year mortality rate was 5.4% (4/74), the lowest reported to date in the literature, with no further increase in the 2-year follow-up period. And while causality cannot be implied because of multiple confounders, Jang *et al* also show that after adjusting for age of onset, baseline assessments and 3-month MRI subtypes, continuing immunotherapy beyond 18 weeks was associated with better CASE scores at 2 years, but continuing immunotherapy beyond 1 year did not confer further benefit.

Going forward, this study calls for a prospective randomised trial of available immunosuppressive therapies. This should also apply to neuromodulatory and immunomodulatory treatments such as vagal nerve stimulation and the ketogenic diet. Future trials will require consensus on many operational definitions such as the duration of NORSE, what constitutes the acute and chronic phase of the illness and better profiling of outcomes, including cognition and neuropsychiatric disability. It is clear that setting up any trial in this subpopulation is very challenging and will require international collaborations. The field of NORSE research and clinical care is evolving fast and it is heartwarming as it is inspiring that concerted efforts are already a reality, spearheaded by the NORSE-Institute[11] with its many collaborating clinicians, families and newly-born national societies. This joint endeavour will for sure allow us to learn from the present to build hope for a future when treating NORSE and better outcomes will become a reality.

Contributors LM the author of the editorial, the sole contributor and guarantor.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Mantoan Ritter L. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2024-334475

Received 25 July 2024
Accepted 3 August 2024

Linked

► http://dx.doi.org/10.1136/jnnp-2024-334285

J Neurol Neurosurg Psychiatry 2024;**0**:1–2. doi:10.1136/jnnp-2024-334475

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