New-onset refractory status epilepticus (NORSE)

- The Role of Metabolic Testing in the Diagnostic Evaluation of Adult NORSE: A Retrospective, Single-Centre Study
- Comparative analysis of new-onset refractory status epilepticus in adult and pediatric patients: immunotherapy timing and functional outcomes
- New Onset Refractory Status Epilepticus
- Outcome of emergency neurosurgery in patients with refractory and super-refractory status epilepticus: a systematic review and individual participant data meta-analysis
- Single-Cell Transcriptomic Analyses of Brain Parenchyma in Patients With New-Onset Refractory Status Epilepticus (NORSE)
- Long-term outcome in new onset refractory status epilepticus: a retrospective study
- Initial Management of Status Epilepticus
- A case of cryptogenic new-onset refractory status epilepticus (NORSE) in which cerebrospinal fluid IL-6 was elevated with increased seizure frequency early in the disease: a case report

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New-onset refractory status epilepticus (NORSE) is a syndrome where status epilepticus manifests in patients who were previously healthy and lack a history of epilepsy or neurological disorders.

Epidemiology

NORSE is seen most frequently in young adults, though all ages can be affected. It does share similarities with other seizure syndromes which occur mainly in children, including Febrile Illness-Related Epilepsy Syndrome (FIRES) and Idiopathic Hemiconvulsion-Hemiplegia and Epilepsy Syndrome (IHHES), so some hypothesize that all may be extensions of a common disorder affecting younger populations [1].

It is difficult to estimate the incidence of NORSE since it is often underreported as status epilepticus attributed to encephalitis. However, one Finnish study on NORSE estimated an annual incidence of 0.7/100,000 and a mortality rate of 36% [2].

Etiology

New-onset refractory status epilepticus (NORSE) is a diagnostically challenging and severe epileptic presentation in which aetiology is an important predictor of outcome.

NORSE often occurs in the background of a preceding upper respiratory tract infection so one hypothesis is it is initiated in response to increased proinflammatory molecules in the brain following viral infection [3] [4] [5].

Pathophysiology

The pathophysiology of NORSE remains unclear, with one study of 130 patients finding 52% of cases (n=67) to be cryptogenic in origin. In cases with an identifiable etiology, the most common was nonparaneoplastic autoimmune, specifically an anti-NMDA receptor antibody, followed by paraneoplastic causes [6].

Diagnosis

Analysis of cerebrospinal fluid in NORSE patients also commonly demonstrated inflammatory pleocytosis, with infectious etiology being the third most commonly identified, although often without an identifiable organism [7]

Treatment

New-onset refractory status epilepticus treatment.

Outcome

Although cases of refractory status epilepticus are rare, they are associated with significant mortality. The prognosis for NORSE survivors is poor as 50% of survivors develop a chronic cognitive or functional disability and often have epilepsy moving forward.

Gaspard et al. estimated that nearly 40% of status epilepticus cases will be refractory to the first and second-line treatments of the aforementioned protocol [8].

The multiple toxicities of antiepileptic drugs have the potential to impart further damage to the already metabolically stressed brain. NORSE patients receive a median of five antiseizure medications during their treatment course yet 77% of cases culminate with administration of continuous anesthetics [9].

This trial-and-error approach may have deleterious effects; therefore, the high morbidity and mortality associated with NORSE may have an iatrogenic component rather than being entirely physiologic. Anesthetic use is particularly concerning since it is associated with poorer outcomes and increased mortality [10].

Retrospective Observational Studies

In a Retrospective Observational Study Kilmer et al. assessed the diagnostic yield of metabolic testing in adult patients with new-onset refractory status epilepticus (NORSE). The primary goal was to determine whether metabolic disorders—particularly inherited ones—contribute to NORSE etiology.

Strengths:

Addresses a relevant diagnostic dilemma in neurologic emergencies.

Longitudinal inclusion of cases over 17 years, potentially capturing rare phenotypes.

Attempts to clarify diagnostic criteria between cNORSE, sNORSE, and PMD-related RSE.

Limitations:

Single-centre design limits generalizability.

Small sample size (42 cases) weakens statistical power.

Retrospective design introduces selection and information biases.

The distinction between RSE and NORSE appears blurred in certain segments, potentially diluting the primary question.

Methods

Demographic, clinical, biochemical, and molecular data were extracted retrospectively. A total of 100 metabolic tests were performed across the cohort. Patients were subclassified into cryptogenic NORSE (cNORSE) and symptomatic NORSE (sNORSE).

Strengths:

Systematic application of a wide range of metabolic tests.

Attempts to correlate phenotype with diagnostic yield.

Weaknesses:

No standardization or protocolized approach to metabolic testing across cases.

Lack of control group (e.g., other RSE etiologies or healthy controls).

Insufficient granularity about the specific tests performed, their thresholds, and criteria for interpretation.

Results

62% cNORSE and 38% sNORSE.

No cases of NORSE were attributed to inherited metabolic disease.

However, three patients with RSE (not NORSE) were diagnosed with primary mitochondrial disease (PMD), and had suggestive red flags: multisystemic features, family history, or characteristic MRI.

Interpretation:

While the negative yield in NORSE patients argues against routine metabolic testing in all adults with NORSE, the positive findings in non-NORSE RSE cases suggest value in targeted testing when certain red flags are present.

Concerns:

The inclusion of PMD-related RSE cases outside NORSE definition might confuse the reader or exaggerate the clinical relevance of metabolic testing in the context of true NORSE.

Conclusion & Impact

The authors rightly conclude that metabolic testing has limited diagnostic utility in unselected adult NORSE, but may be relevant when specific clinical, radiological, or familial features suggest mitochondrial disease. The study supports a more selective approach to metabolic investigations, reinforcing the need for clinical pre-screening tools.

However, the findings are hypothesis-generating rather than definitive, and the study lacks sufficient statistical rigor or sample diversity to guide practice definitively. [11].

Case series

In a descriptive, semiprospective review of all cases of NORSE syndrome seen between 2000 and 2004 at a tertiary care public hospital in Singapore. A review of the literature was performed to identify possible additional similar cases for comparison.

Seven patients with NORSE syndrome were identified. Characterizing features were female gender, young age, previous good health, cerebrospinal fluid pleocytosis (in 4), antecedent febrile illness (in 5), extraordinarily prolonged status epilepticus (average 32 days), failure of extensive investigations to reveal an underlying cause, the catastrophic outcome as well as temporal lobe and leptomeningeal abnormality on brain magnetic resonance imaging. A review of the literature identified 12 similar patients, comprising both adults and children.

Based on these patients and those described in the literature, they characterized the NORSE syndrome. Increased recognition of this clinical entity is needed to help delineate the underlying etiology of this unique severe illness [12].

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