NORSE/FIRES ANNOTATED REFERENCE LIST
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Articles are categorized as follows:
I. Terminology/Definitions/Guidelines/Consensus statements
II. Original Research
III. Systematic Reviews/Meta-analyses
IV. Other Reviews
V. Case Series
VI. Case Reports
VII. Articles in Lay Media
VIII. Personal Narratives

Within each category, articles are listed most recent first. Some of the most important/highly recommended manuscripts are highlighted in bold. About 130 articles are included in total.

The following icons, representing the type of publication or aspect of disease/science that the paper addresses, are used to label many of the references.

Pediatrics 🌸

Etiology/Pathogenesis 🍝

Imaging 🌌

Anesthesia 🦢

Ketogenic diet 🥑

Immunotherapy 🍀

Original Research 🔌

Outcomes 🧠
I. Terminology/Definitions/Guidelines/Consensus Statements


An international multidisciplinary group of experts convened (FIRES workshop) to propose a protocol for evaluation and management of FIRES. The group recommended early administration of ketogenic diet and IL-1R antagonist anakinra (that blocks biologic activity of IL-1beta), once FIRES was suspected.


An international multidisciplinary group of experts develop proposed consensus definitions of NORSE and FIRES, and related conditions and terms.


AES guideline for management of convulsive status epilepticus in adults.


A short review and delineation of FIRES and IHHE (idiopathic hemiconvulsion, hemiplegia, and epilepsy syndrome)

(Review- 2013)


FIRES case report and review of literature; authors suggest that AERRPS, DESC, NORSE and FIRES may be the names used for possibly the same entities.
II. Original Research

A retrospective study of 92 children with NORSE showed that majority of pediatric patients with NORSE present with FIRES. The clinical features, EEG, neuroimaging and prognosis were not significantly different between the FIRES group and non-FIRES group. The presence of SRSE, diffuse cortical edema and multifocal abnormality was related to a poor prognosis.


In this study of 26 cases of 'NORSE', there was no difference in prognosis between 'NORSE' and non-'NORSE' RSE, nor in any sub-analysis in the 'NORSE' cohort.


A retrospective cohort study aiming to evaluate and incidence and predictors of epilepsy after antibody positive autoimmune encephalitis concluded that although 80% patients have acute seizures about 40% develop epilepsy and early initiation of immunotherapy may lower this incidence.


A prospective cohort study of 46 NORSE patients aiming to evaluate the significance of the relationship between fever onset and status epilepticus found that those children with onset of fever more than 24 hours prior to the onset have distinctive clinical features and worse outcomes.

This retrospective multicenter study from US and Canada aiming to study the benzodiazepine administration patterns in pediatric refractory convulsive status epilepticus found that failure to escalate to non-benzodiazepine ASMs occurs mainly in out-of-hospital RSE onset.


This survey-based study of parents of children with FIRES showed that despite their children’s significantly impaired functional outcome after FIRES and high rates of medically refractory epilepsy, the cohort demonstrated remarkable emotional resilience; they perceive social media as beneficial and are interested in social media-advertised research.


Six clinical features (previous good health, prodromal fever, lack of psychobehavioral/memory symptoms, absence of dyskinesias and symmetric brain abnormalities) were used to create a score and patients with status epilepticus with prominent motor features and a high score were more likely to have cryptogenic NORSE.

A single-center retrospective study from Texas looking at etiology, clinical presentation, therapies, and outcomes in 40 children with NORSE found that in more than half of the children the etiology remained cryptogenic and no children had neuronal antibodies detected.


A retrospective study of various features of the disease in 26 patients with NORSE, limited to cases with super-refractory SE, which they called “NOSRSE”. Seven patients underwent biopsy, autopsy, or both, which was diagnostic in three- herpes simplex encephalitis, candida encephalitis and acute disseminated encephalomyelitis.


Editorial to Matthews et al NORSE study above.


Retrospective study of a 20-patient adult cohort describing etiology, clinical features, and outcome in 20 patients with NORSE. Most were cryptogenic, with high mortality and subsequent intractable epilepsy was common.


Exome sequencing in 50 individuals (29 patient-parent trios and 23 single probands) with FIRES showed no pathogenic variants in genes known to be associated with epilepsy or neurodevelopmental disorders; no HLA allele were found in 29 patients sequenced.


A prospective cohort study aiming to identify if immunostaining of serum/CSF is a marker of progression to SRSE and poor outcomes; they did not find significant differences between the groups with and without immunostaining.

_This study showed that children with FIRES may have impaired TLR3, TLR4, TLR7/8 and TLR9 due to either defective phagocytosis or T cell regulatory dysfunction. These were compared against children with febrile seizures and non-refractory epilepsy._


_Long-term outcome of 39 patients with NORSE. Predictors of poor functional outcome and pharmacoresistant epilepsy included leptomeningeal enhancement on initial MRI and hippocampal atrophy on later MRIs._


_A retrospective cohort of 25 children treated with Anakinra for FIRES. Anakinra was potentially safe with treatment discontinuation in only one child due to infection. Earlier initiation of Anakinra was associated with better outcomes._


_A retrospective multicenter study of SRSE including 68 subjects treated with ketamine showed an association with decrease in seizure burden. The data supported the notion that high dose ketamine infusion is associated with decreased vasopressor requirement without elevation in intracranial pressure._

A retrospective study of 25 children with FIRES showed that 16% children died in hospital, most children developed refractory epilepsy and significant decline in function at hospital discharge, but there was improvement upon long term follow up.


A retrospective cohort study of outcomes in 40 children with RSE treated with pentobarbital infusion showed 30% mortality in this group but despite prolonged pentobarbital infusion, there were cases of good neurologic outcome.


A retrospective study of 29 patients with FIRES showed that common acute complications include liver dysfunction, arrhythmias, and skin breakdown. Higher grades of periventricular white matter changes suggested poor outcome.


Retrospective study of 12 patients, including 21 PET scans and 50 MRI scans during their hospitalizations showed PET abnormalities were very common and could be markers of disease activity.


A prospective case-control study (7 FIRES/10 controls) suggesting that FIRES is associated with reduced expression of intracellular IL-1RA isoforms and functional deficiency in IL-1RA inhibitory activity.

In this prospective observational study, on serial imaging, brain atrophy was seen in all 19 patients with SRSE despite use of anti-seizure medications, the degree of atrophy appeared to be related to the duration of SE. There was no correlation of atrophy with clinical outcome at discharge or follow up visits.


In this prospective swiss cohort of 804 SE (33% RSE and 4% SRSE) episodes, SRSE tended to occur in younger patients with no history of epilepsy and was associated with a high mortality.


This prospective multi-center observational study aiming to compare the use of therapeutic coma between two health systems from North America vs Europe found that local practices in terms of anesthesia for RSE vary but that the use of anesthesia does not affect outcome.


Largest series (n=130) of NORSE cases via retrospective review from 13 medical centers found that 50% of cases have a possible or likely identifiable cause, mostly autoimmune or paraneoplastic encephalitis, most survivors (92%) remained on anti-seizure medications and 37% developed epilepsy.


This prospective case control study showed that proinflammatory cytokines (IL-6) and chemokines (IL-8/CXCL-10) were selectively upregulated in AERRPS (FIRES). In contrast, most T-cell-associated cytokines (IL-2, IL-17A, etc) and homeostatic chemokines (CCL21, CXCL12, etc) remained unchanged or were downregulated. These were compared against other inflammatory
neurological disorders and a group with non-inflammatory neurological disorders. The study thus provided strong suggestion towards involvement of innate immunity in pathogenesis of FIRES.


Retrospective study of role of immunotherapy in 11 patients with NORSE and a pooled analysis of case series from literature suggested that those receiving immunotherapy likely do better than those who do not.


Serum and CSF samples were tested in 140 patients with refractory status epilepticus with antibodies to unknown neuropil antigens. Cell based assay showed high antibody titers in serum/CSF of 6 patients. High titres of serum and CSF GABAA were found to be associated with a syndrome of severe encephalitis with seizures and refractory status epilepticus.


A retrospective study looking at outcomes after pentobarbital infusion for management of SRSE in 31 patients.


This retrospective case-control study of patients treated with high (median: 0.4 mg/kg/h) vs. low-dose (0.2 mg/kg/h) midazolam found that higher doses were associated with better SE control and lower mortality, despite more frequent hypotension.

In this retrospective cohort study of mortality of SRSE in a developing country like India showed that out of 30 SRSE patients, two-thirds of patients survived and one third had a good outcome.


A multicenter retrospective study of ketamine use in 58 instances of refractory status epilepticus that showed that ketamine was safe and relatively effective in the management.


A 20-patient series describing the clinical phenotype of GABAB R Ab to include limbic encephalitis, ataxia, opsoclonus-myoclonus syndrome and status epilepticus. These were observed to usually respond to treatment although the long-term prognosis is determined by presence of a tumor.


This retrospective study of 63 subjects found that good outcome was still possible despite prolonged therapeutic coma (at times for months) for prolonged, super-refractory SE that was defined as SE persisting despite one week of induced coma.


Despite phenotypic similarities with certain genetic epilepsies, extensive genetic analysis for the candidate genes PCDH19, SCN1A or POLG mutations was unrevealing.

Retrospective multicenter study of 77 children with NORSE found that no therapeutic agent was efficacious in shortening the acute phase, with the possible exception of a ketogenic diet.


This randomized controlled trial compared propofol and barbiturates for the treatment of refractory SE. It was aborted due to low enrollment rate. Efficacy of the two drugs was similar but barbiturates were associated with a longer intubation time.

III. Systematic Reviews/Meta-analyses


A systematic review of efficacy and safety of ketogenic diet in refractory and super-refractory status epilepticus. The diet was found to be effective and side effects mild.


An eight-patient series and systematic literature review of ketogenic diet treatment (KDT) for management of SRSE suggested that KDT is feasible and safe and early initiation has the potential for efficacy in about two thirds of patients with SRSE.


A systematic review of all NORSE and FIRES cases published between 2003-2019 summarizing the clinical neurophysiological, imaging, treatment, and outcome data. This study showed that 70% of adult NORSE have abnormal MRI at presentation while 61% of pediatric FIRES had normal MRI at presentation.

In this systematic review of literature of FIRES treatments and outcomes that had most patients from Asian countries, a positive outcome had an association with use of ketogenic diet.


Authors conduct as systematic review of various anesthetic treatments for refractory and super-refractory status epilepticus. The study includes limited outcome assessments for each of the therapies included. They define the entity of super-refractory SE make broad recommendations regarding optimal therapy.


This review of literature from 1990-2008 found more than 180 unusual causes of status epilepticus. They could be organized into four main categories: inflammatory, infectious, genetic, and toxic or drug-related

IV. Other Reviews


A comprehensive review of current literature on NORSE/FIRES that includes flow diagram for evaluation and management of NORSE/FIRES (reproduced from NORSE institute).


A review discussing the role of different components of immune system in various types of acute seizures and epilepsy including NORSE/FIRES.

3. Lin, W.-S., Hsu, T.-R. Hypothesis: Febrile infection-related epilepsy syndrome is a microglial NLRP3 inflammasome/IL-1 axis-driven autoinflammatory syndrome (2021) Clinical and Translational Immunology, 10 (6), art. no. e1299.
By a review of literature authors here hypothesize that of overactivation of microglial NLRP3 inflammasome/interleukin-1 axis is the driving event in FIRES by creating a proinflammatory and proconvulsive milieu.


A comprehensive review of various treatment options for SRSE.


A review of literature Anakinra use in children with FIRES and drug resistant epilepsy showed marked improvement in some patients with FIRES and most patients with drug resistant epilepsy.


A case report with review of literature discussing the feasibility and practical issues of use of ketogenic diet for status epilepticus.


Paper informing health care providers of the NORSE/FIRES family registry created by the NORSE institute. Patients or their medical team anywhere in the world can directly enter their data into the registry and continue to enter long term data.

A review of clinical features, terminology, diagnostic challenges, therapeutic options for FIRES.


   A review of NORSE/FIRES management.


   Narrative review summarizing clinical features, suggested evaluation, treatment and prognosis in NORSE/FIRES.


   A review of all aspects of FIRES as stated for the review above.


   A narrative review of NORSE/FIRES and a call for multi-center international collaboration, proposal of future research directions.

   (Future directions/research initiates)


   A review article published in Jan 2018, where nine experts discuss the proceedings of the first international NORSE/FIRES symposium that include consensus definitions, pathophysiology, possible biomarkers, therapies, and future directions of research.

A narrative review discussing various antibodies as a cause of encephalitis and their varied clinical and radiological presentations.


*Narrative review of literature to support authors’ view that FIRES and IHHS are conditions where the status epilepticus is mediated by inflammation.*


*A review of potential therapies and suggestion of a protocol/flowchart for management of SRSE.*

V. Case series


*A 5-patient case series describing the histopathological findings in adults with NORSE.*


*Long term follow up of six FIRES patients suggesting survivors experience a significant loss of functional independence due to seizures, cognitive dysfunction.*

In this series of six children treated with intrathecal dexamethasone (ITD) for FIRES, it was observed that ITD could shorten the critical stage of the disease. There was a significant reduction in select CSF cytokines/chemokines (such as CXCL-10, neopterin) following treatment but not all (such as IL-6, IL-8, IL-1beta) that were elevated prior to ITD (compared to epilepsy patients as controls).


A retrospective observation study of perampanel in 20 patients with drug resistant epilepsy and FIRES, where perampanel was used for three children with FIRES and seizures stopped within a day on days 19 and 32 of hospitalization.


This 7-patient series studied the efficacy of ketogenic diet in 10 pediatric patients presenting with FIRES. All 10 patients achieved ketosis in 24-72 hours. SE was controlled in 8 patients within 2-19 days of initiation of KD, one had serious adverse effects (V.fib).


A 7-patient retrospective case series of NORSE describing the etiology, clinical and EEG characteristics, treatment response and outcomes.


A 13-patient series of NORSE with limbic encephalitis observed that on follow up imaging 10/13 had extra-temporal lesion extension, most commonly to claustrum. Lesion extension was associated with poor outcome.


A two-patient series with an observation of good outcomes with early immunotherapy (steroids, IVIG and plasmapheresis).


Experience with tocilizumab in 7 NORSE patients who were refractory to conventional immune therapy. Good response was reported in 6/7.


Editorial for the tocilizumab paper above.


Retrospective multicenter case series of 10 patients managed for SRSE with ketogenic diet.


A 5-patient series with an observation of good outcome with early immunotherapy (steroids and IVIG).

A 13-patient European series of antibody mediated status epilepticus observed that this condition was severe but potentially reversible and long duration did not necessarily imply fatal outcome.


A three-patient series of experience with plasma exchange in cryptogenic NORSE.


One of the early case series (2003) describing the clinical course of six adults with NORSE/FIRES.


In this 6-patient series, authors propose that the etiology of NORSE is likely heterogeneous, with a proportion being non-infectious. The paper includes the first detailed list of tests that should be performed to identify a potential cause.

VI. Case reports


15. L’Erario M, Roperto RM, Rosati A. Sevoflurane as bridge therapy for plasma exchange and Anakinra in febrile infection-related epilepsy syndrome. *Epilepsia Open*. 2021. *A report of use of sevoflurane as a bridge to immunomodulatory treatment for a child with FIRES.*


*A report of a six-year-old child with FIRES with a robust response to anakinra after failing high potency anesthetics and multiple other treatment modalities. Anakinra was maintain for a year until this report and was tolerated well with infrequent seizures.*


Case report and a review of nursing care needs in patients with FIRES.


A single patient report showing microdialysis could help determine the depth of burst suppression to a degree that leads to a normalization of cerebral metabolic markers


Report of a 6-year-old child with FIRES refractory to Anakinra then treated with ketogenic diet and tocilizumab.


Report of a 14-year-old girl with FIRES and a robust response to two cycles of 4 mg/kg of Tocilizumab.


Case report of a 29-year-old male with FIRES and an early neuroradiological finding of reversible splenial lesion.


Case report of FIRES with chronic use of Anakinra for relapse prevention.


VII Articles in Lay Media


3. Wong N. Loving My Son, After His Death - The New York Times (nytimes.com)

VIII Personal Narrative


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